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Ontario

ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.

Hearing held in Court Room 20
Court House
361 University Avenue
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

Commissioner

P.S.A. Lamek, Q.C.

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

Transcript of evidence
for

July 7th, 1983

VOLUME 9

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Court House, 361 University
Avenue, Toronto, Ontario, on
Thursday the 7th day of July,
1983.


- - - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOT - Registrar

- - - - -

APPEARANCES:

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L. CECCHETTO)	General and Solicitor
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R. DEVINS)	Sick Children
R. BATTY)	
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	Children
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	Nurses' Association of Ontario
	and 35 Registered Nurses at
	The Hospital for Sick Children



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1 APPEARANCES: (Continued)

2 H. SOLOMON Counsel for the Ontario
3 Association of Registered
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4 W.A. BOGART Counsel for Susan Nelles -
Nurse
5 G.R. STRATHY) Counsel for Phyllis Trayner -
6 P. RAE) Nurse
7 M. ROSENBERG Counsel for Sui Scott - Nurse
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10 S. LABOW Counsel for Mr. & Mrs. Gosselin,
11 Mr. & Mrs. Gionas, Mr. & Mrs.
Inwood, Mr. & Mrs. Turner, and
12 Mr. & Mrs. Lutes (parents of
deceased children)
13 F.J. SHANAHAN Counsel for Mr. & Mrs. Dominic
Lombardo (parents of deceased
14 child Stephanie Lombardo)
15 W.W. TOBIAS Counsel for Mr. & Mrs. Hines,
(parents of deceased child
16 Jordan Hines)
17 J. SHINEHOFT Acting for Lorie Pascia and
Kevin Garnett (parents of
18 deceased child Kevin Pascia)
19
20
21
22
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/DP/ak

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2

---Upon commencing at 10:00 a.m.

3

DR. STEVEN SOLDIN, Resumed

4

THE COMMISSIONER: Yes, Miss Cronk.

5

MS. CRONK: Mr. Commissioner,

6

Dr. Soldin has provided me over the break with a

7

hard copy, if you will, of the slides which he

8

referred to yesterday morning in his evidence, and

9

I would like to propose that they be marked this

10

morning as an exhibit.

11

THE COMMISSIONER: Exhibit 26.

12

---EXHIBIT NO. 26: Hard copy of slides presented
by Dr. Soldin, July 6th, 1983.

13

14

MS. CRONK: The first two slides

15

that he referred to, sir, are reproduced on one page

16

of an extract. I think it can best be identified

17

by - it is page 6 from Therapeutic Drug Monitoring

18

Journal, Volume 3, November 1, 1981. That is

19

inclusive of the first two slides, and the second
document is a reproduction itself of the third slide

20

to which he referred and that is described as

21

Figure 1, Theophylline Concentration.

22

THE COMMISSIONER: Which concentra-
tion?

23

MS. CRONK: That is the difficulty.

24

I think it is theophylline. Is that right?

25



1

2

THE WITNESS: Theophylline.

3

THE COMMISSIONER: That is spelled ---

4

MS. CRONK: T-h-e-o-p-h-y-l-l-i-n-e

5

concentrations.

6

THE COMMISSIONER: Do they all go

7

in as one exhibit?

8

MS. CRONK: That would be fine,

9

Mr. Commissioner. Copies have been provided to
counsel this morning, sir.

10

In addition, you will recall,

11

Mr. Commissioner, the request was made yesterday

12

by various counsel for Dr. Soldin to reproduce in

13

a typewritten form the data to which he referred

14

yesterday in reporting upon the digoxin readings

15

that he obtained, ante mortem, on the group of

16

children who had been known not to have received

17

digoxin and, in addition, the group of patients

18

who were known to have received digoxin, the two

19

categories; and in addition the third category of

20

post mortem testing that he did inclusive of

21

patients both on and off digoxin.

22

Dr. Soldin has advised me that in

23

respect of the second category, the ante mortem

24

testing on children, patients who were known to have

25

been on digoxin, the tabulated results of that in



1
2 fact are set out in the memorandum that was filed
3 yesterday as an exhibit, copy of Dr. Soldin's
4 memorandum to Dr. MacLeod, and that is the only
5 place where those results, I understand, have been
6 tabulated.

7 He has undertaken to have the data
8 in respect of the other two comparative series of
9 tests tabulated. They are not in a finalized form
10 As soon as they are I will have them reproduced and
11 distributed amongst counsel, and marked as an exhibit
at that time.

12 Thank you, sir.

13 THE COMMISSIONER: Mr. Bogart, are
14 you first?

15 MR. BOGART: Sir, I do not believe
16 that I have any questions of this witness, but I wish
to make one remark, if I may.

17 THE COMMISSIONER: Yes.

18 MR. BOGART: That is, as you know,
19 sir, I have shown some interest in a list that was
20 compiled by Dr. Ellis and have gone through it in this
21 evidence at the Preliminary Inquiry, Volume 13,
22 beginning at page 12 to page 35.

23 My understanding of the transcript,
24 sir, is that he compiled 2 lists. One was autopsy
25



1
2 samples and I have been told by Miss Cronk in our
3 meeting yesterday that Dr. Phillips will called in
4 respect of those readings.

5 In respect to the pre-mortem samples,
6 I have been told by Miss Cronk that Dr. Soldin is
7 not the witness who should be asked about these, and
8 that Miss Cronk is making enquiries of the Hospital
9 concerning who will be in a position to answer my
10 questions about the readings that were taken.

11 On that basis, I have no questions
12 of this witness.

13 THE COMMISSIONER: All right,
14 thank you. Do you confirm all that?

15 MS. CRONK: That is correct, sir.

16 THE COMMISSIONER: Thank you.
17 Mr. Strathy?

18 CROSS-EXAMINATION BY MR. STRATHY:

19 Q. Doctor, I would like to begin
20 by asking you about the methodologies for the
21 detection of digoxin that we have been hearing about.
22 To date I think we have heard of three methods: the
23 RIA method; the FPIA method and the HPLC method, if one
24 can call it that at this point.

25 Let me start with the RIA method. As
I understand it, sir, it has been in use generally



1

2

3

4

in North America for about 10 years and at the
Hospital for Sick Children since about 1974. Am I
right?

5

A. That is correct.

6

7

Q. If you could have Exhibit 25
in front of you, that was your memorandum to
Dr. MacLeod.

8

9

A. Yes.

10

MR. STRATHY: Mr. Commissioner, do you
have a copy of that?

11

12

13

THE COMMISSIONER: Yes, I have,
thank you. I am very well treated now. I have this
book with all the exhibits in it.

14

15

16

17

18

19

MR. STRATHY: Q. Looking at the last
page of that memorandum. I gather, Doctor, that that
reflects a survey that was done of a number of
laboratories in North American concerning their
results of digoxin testing? Quality control samples
are sent out to each laboratory and analyzed and then
the results tabulated in this format.

20

21

A. This is a survey that is done
on a monthly basis.

22

23

24

Q. Who is it that does the survey?

A. The American Association for
Clinical Chemistry - the Therapeutic Drug Monitoring
Program for that Association.

25

Q. And your Hospital is a member
of that?



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A. We subscribe to that program.

Q. Are the laboratories to which these are sent, or the tests are sent from, are they all hospital laboratories?

A. No. Some would be private laboratories - any laboratory offering digoxin analysis could subscribe to this program. The majority are probably hospital laboratories.

Q. Looking at the bottom left hand corner of this chart, Exhibit 25, do you have that in front of you?

A. Yes. - bottom left hand corner?

Q. Bottom left hand corner.

A. Yes.

Q. It appears to indicate that RIA is in use at the present time at least by the vast majority of the laboratories that contributed to the survey?

A. Right.

Q. In fact, some 312 of the 404?

A. Yes.

THE COMMISSIONER: I would like to know how you calculate that - how you figure that? Am I looking at the same chart?

MR. STRATHY: Mr. Commissioner, it is the last page of Exhibit 25, in the bottom left hand corner.



1

2

THE COMMISSIONER: Yes, yes, I

3

understand.

4

MR. STRATHY: There is a reference

5

to all labs, 404.

6

THE COMMISSIONER: I was looking

7

at the wrong chart. Thank you.

8

MR. STRATHY: And 312 of those are

9

using RIA.

10

Q. Now, as I understand it,

11

Doctor, the RIA technique was developed and designed

12

for the therapeutic monitoring of digoxin in a

13

clinical setting. Am I right on that?

14

A. That is correct.

15

Q. That was when it was invented,

16

if you will, in 1969 or 1970?

17

A. Yes.

18

Q. That was the purpose of the

19

invention, and that is the use to which it has been

20

put since that time.

21

A. Mainly, yes.

22

Q. And we have, as we have seen,

23

these kits which are designed for that very purpose?

24

A. Right.

25

Q. And the Hospital for Sick

Children, instead of using a kit, instead of buying



1

2

the cake mix, you make your cake from scratch,
basically?

3

4

A. Right.

5

Q. But the principles are exactly

6

the same?

7

A. Yes.

8

Q. I take it from your evidence

9

that you essentially consider the RIA method to be
a realiable and useful method for the purposes for
which it was designed?

10

11

A. I do.

12

Q. And perhaps the only qualification

13

you would have to that is that it perhaps may not
be as specific as it might be with respect to the
detection of substance X.

14

15

A. That is correct. I think one

16

has to have another - either, provided it is

17

appropriate, the test is appropriately done, and

18

there is also the reliable, in my opinion, by the

19

RIA technique.

20

As you will note, in the handout that

21

you are referring to, there are many labs that appear

22

to be performing poorly, and they are also using the

23

RIA technique, so that is another factor.

24

25



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Q. So, just looking as you point out then to the bottom of the page under RIA, you have some labs using that technique reporting as low under the column "Min", as low as .42 and other labs reporting as high as 11.79?

A. That's right.

Q. When, according to this, the target, what they should have found in the perfect world would have been 3.80?

A. Correct.

Q. So, what you're saying is, there can be a tremendous variation in the results if the test is not properly administered?

A. That's right, yes.

Q. But I take it you agree with me with the further qualification that it's not as specific as it might be with respect to Substance X?

A. Yes.

Q. And if I can put it in somewhat imprecise terms, I take that when you are using an immunoassay procedure, one of the things that you want is specificity. Specificity equates to good in terms of immunoassay, it's a good thing?

A. Right.

Q. The less specific the assay is, the more it's possible that it will pick up things



B.2

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other than the substance for which it is designed?

3

A. Yes.

4

Q. Now, turning then to the second

5

methodology that you have I think been the first

6

witness to give any significant evidence about, FPIA.

7

As I understand it, Doctor, the FPIA, or the

8

Fluorescence Polarization technique is something that

9

has been used in biochemistry for some considerable

10

period of time. Not in terms of digoxin, but the

11

technique itself?

A. Yes.

12

Q. Can you give us an idea of how

13

long it has been in use?

14

A. Approximately 50 to 60 years. The

15

thoughts were first written down some 50 to 60 years

16

ago.

17

Q. So, it's a technique that chemists

18

or biochemists such as yourself are familiar with

19

and have used for some time?

20

A. It's a technique that some people

have used for some time, yes.

21

Q. You are qualifying that. I take

22

it you haven't used it for some time?

23

A. That's correct.

24

Q. But I gather from what you have

25



B.3

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2

said, it is only reasonable that the test has been
defined or developed for purposes of digoxin?

3

4

5

6

A. For the purposes of drug
analysis, measurement of drug concentrations by
digoxin, being one drug is just part of the spectrum.

7

8

9

Q. So, is it in recent years the
detection has been used for drugs?

10

11

12

A. Yes, in the last four years
perhaps.

13

14

15

Q. And the Hospital for Sick
Children has now had FPIA for digoxin for about four
or five months?

16

17

A. Three or four months, yes.

18

19

20

Q. And I gather very soon you are
going to be doing all your digoxin testing using
this methodology?

21

22

23

24

25

A. I think in two to three weeks
probably, yes.

Q. Now, is it fair to say that this
FPIA method is also designed and intended for the
therapeutic monitoring of digoxin in a clinical
setting?

A. That's correct.

Q. And I take it from your evidence
that you consider it to be a reliable and useful



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procedure for the detection of digoxin in that setting?

A. That's correct, yes. It is the state of the art, perhaps.

Q. I take it from that that you mean, and I have gathered from your evidence, that you consider it perhaps to be a somewhat better procedure than RIA, both in terms of its efficiency and in terms of the precision of its results? I don't want to take you too far on that point because ---

A. They are both good procedures I think. I think we went into this yesterday. I have some slight preference for the FPIA method, yes.

Q. Do I understand correctly from your evidence that it, like the RIA, has the same problem with respect to Substance X, that is that there is a specificity problem and even FPIA may show up Substance X?

A. Yes.

Q. But perhaps not as much as the RIA method?

A. Right.

Q. Now then, turning to HPLC. I understand from your evidence that you yourself have never used that for digoxin?

A. I have never used it for digoxin.



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Q. But looking at your curriculum vitae, and I won't ask you to pull it out, but it does seem to me as though you've had considerable experience with HPLC in the clinical setting?

A. Yes.

Q. And just to be sure that I understand, there are references to a number of articles that you've written, lectures that you have given pertaining to HPLC, and sometimes it is referred to as High Performance Liquid Chromotography. Is that the same thing as high pressure?

A. The same thing, right.

Q. So, you do have a considerable, if you will, and it's an expression I don't like, but hands-on experience with HPLC?

A. Right.

Q. Now, as I understand it, and I'm going to put this in fairly simplistic terms, but as I understand it, HPLC involves two sets. It involves firstly a separation procedure where you separate out the substance which you wish to analyze. Is that an accurate statement?

A. One performs any chromatographic analysis essentially to separate the components of a mixture. So, you have several things and you wish to separate them.



B.6

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Q And the thing that you separate off is called a fraction?

3

4

A Well, you can collect fractions from the common element.

5

6

Q Perhaps if I can tell you what I understand the second step to be and you can perhaps put the whole thing in context. I was going to say that having done the first step of separating, you then measure the thing that you have separated off?

7

8

9

10

A Right. In other words, first you separate the compounds and then you have to detect the compounds. So, you need a detecting device at the end of the common ...

13

14

Q Now, when you talk about detecting, are we talking about the detecting levels in the same way as we have in HPLC - I am sorry, in the same way as we have in RIA?

15

16

17

A Yes, detecting concentrations of a drug. It is a better word than levels.

18

19

Q All right, fair enough. So, there is basically then a two-step process, a separation and the detection of concentrations?

20

21

22

A Right.

23

Q I believe you were present in the room for the evidence of Mr. Cimbura?

24

25



B.7

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A. For most of that evidence, yes.

Q. Well, I wonder if you heard his evidence with respect to the procedure that he used concerning HPLC. Let me at least put to you what I understood his evidence to be. As I understood what Mr. Cimbura did, it was that he did the first step, that is, he used HPLC to perform the separation but he did not then go on to use that same methodology for detection, he used RIA for detection?

A. Well, you cannot use HPLC for detection, you have to use some form of detector. Now, there are other different types of HPLC detectors. One would be RIA, okay, at the end of the procedure.

Q. Well, do I understand it then that an HPLC method would have its own type of detector or would you simply couple it onto some other detector system?

A. Essentially when one develops an HPLC procedure, one looks at the molecule that one wishes to identify, quantify, and makes a decision as to what type of detection system would be most appropriate. It may mean that one would want a fluorescent detector or a spectrophotometer or an electric chemical detector, or maybe, as Mr. Cimbura chose to use, a radioimmunoassay as a detecting device essentially.



B.8

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Q. So that having gone through
HPLC then, there are a number of different detection
devices that you can employ?

A. Yes.

Q. Now, as I understand it, HPLC
never has been in use at the Hospital for Sick
Children for the monitoring of digoxin?

A. No.

Q. And you can look at our chart
on Exhibit 25, it appears that there was one
laboratory using HPLC, at least one laboratory
responding, providing the information - one laboratory
using HPLC. Am I right about that?

A. You're right, yes.

-



C/DM/ak

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Q. And do you happen to know which laboratory that was?

A. No, I don't.

Q. You don't know whether it would be Mr. Cimbura's laboratory?

A. I don't know. I am not - I don't - I assume that he wouldn't be a member of this program, this is a program for clinical laboratories and not for forensic laboratories.

Q. All right. Looking in any event at those figures beside that HPLC under column "Min" and "Max", it would appear that that laboratory simply submitted one response that its finding was 6.40.

A. Correct.

Q. When it should have been a finding of 3.8?

A. Yes.

Q. So in that particular case there was a fairly wide variance from the target using HPLC?

A. Correct.

Q. And I suppose you can't really tell us whether that was due to the method itself or the skill with which it was performed?

A. No, I have no comments to make



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on that. Other than that I personally would never
use HPLC for the routine monitoring of digoxin in
any hospital laboratory at the present time.

5

6

7

8

Q. And I gather from your evidence
there were several reasons for that. One being
that it is a very time consuming procedure, is that
right?

9

10

A. It is time consuming. The
protection devices they are simple, and that are
available and they lack sensitivity.

11

12

Q. I am sorry, what was that about
sensitivity?

13

14

15

16

A. The detection devices that are
available lack the type of sensitivity that is
required in order to do therapeutic drug monitoring
easily and rapidly on patient samples.

17

18

Q. You mean the detection
methodologies to be used with HPLC lack the
sensitivity?

19

A. Correct.

20

21

THE COMMISSIONER: I am sorry, you
lost me. I thought we didn't have any detection
devices with HPLC?

22

23

24

25

THE WITNESS: No, those devices
that are used together with HPLC. HPLC is used in



C3 1
2 the first step to separate digoxin from the other
3 compounds and you can detect it. If you use a
4 spectrophotometer, we say the sensitivity is not
5 appropriate for clinical samples. So you could
6 choose RIA which was the choice of Mr. Cimbura and
7 that certainly is a sensitive procedure. That then
8 would mean that every sample has to be analyzed
9 both by HPLC followed by radioimmunoassay and it is
10 very time consuming and it just doesn't lend itself
11 to the routine monitoring of digoxin in a hospital
laboratory.

12 It is important in our clinical
13 setting to ideally get a result back very quickly
14 so that appropriate changes in the doses regimen
can be made.

15 MR. STRATHY: Q. Just so I am
16 sure of this. You talk about the detection systems
17 and you mentioned a spectrophotometer I believe.
18 Is it fair to say that RIA is not usually used as
19 a detection system with HPLC?

20 A. It is sometimes used, but
21 rarely.

22 Q. What would you more often be
23 using with HPLC?

24 A. The most common detector is a
25



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spectrophotometer, then fluorescence probably the next
most common, and electrochemical, the third most
common.

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Q. Thank you. Now, I gather that
HPLC suffers from the same problem with respect to
substance X as FPIA and RIA do. Let me start with a
question on these. As I understand it with HPLC
you can only separate out two substances, or three
substances if you know to begin with what those
substances are? In other words, you have standards
of various substances and you run them through the
system to begin with.

13

14

15

16

A. I think with HPLC you can
carry out separation of compounds, they may be known
and they may be unknown. You wouldn't be able to
identify the unknowns unless you have a standard.

17

18

19

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21

22

23

Q. All right. So if you were
trying to separate out digoxin from substance X you
would have to have a standard for substance X before
you did that, before you could do that reliably?
You can't be sure that what you have coming off is
only digoxin and not digoxin and substance X unless
you have been able to identify substance X and
run it off?

24

25

A. Yes. Let me answer that



1
2 question, this is a hypothetical question.

3 Q. Yes.

4 A. Let us assume that we are
5 injecting into the chromatogram a mixture of digoxin
6 and substance X, and let us assume that they are
7 separated under the system of analysis that we
8 chose to use in the chromatography. We would then
9 get two peaks eluding from that column, right,
10 which could be identified and they could be
11 identified by the radioimmunoassay for example. So
12 that way we would be able to show under this hypo-
13 theoretical sample that one of those peaks corresponds
14 to digoxin, and the other peak doesn't correspond
15 to digoxin but does cross-react with the antibody.
16 That would be a stronger indication that that other
17 peak is the compound we are interested in.

18 Now, at this point in time we don't
19 have a standard ---

20 Q. Exactly.

21 A. --- for that compound. So if
22 they separated and if one could identify these
23 two peaks with our detecting system whatever detector
24 we chose, then we would be in a good position to
25 carry on further studies to attempt to identify the
structure of compound X, or substance X, but if they



1
2 didn't separate, which is the next step, then you
3 would have no way of saying that the HPLC system
4 with RIA detection has in fact separated substance X
5 from digoxin.

6 Q. So you are talking purely in
7 a hypothetical sense then?

8 A. Right. In my opinion in order
9 to achieve that identification, assuming substance X
10 was very similar to digoxin and ran identically with
11 digoxin in the chromatogram, one would have to use
a different detector.

12 Q. A different detector than?

13 A. Than radioimmunoassay. So
14 the detection system that would have to be used in
15 my opinion would be mass-spectrometry, and if you
16 combined HPLC with mass-spectrometry you could then
17 with certainty say that that alluding peak is or
18 is not pure digoxin. You would also, in my opinion,
be able to identify substance X quite quickly.

19 Q. So what you are telling us then
20 is, and I gather what you have given us is reasonable
21 shorthand of what you would actually do. What you
22 are telling us is that there is a way in which you
23 as a biochemist would go about using HPLC and mass-
24 spec to separate out substance X from the digoxin in
25



1

2

any particular sample? There is a way it could be
done?

3

4

A. That is the way I would approach
this problem.

5

6

Q. If you were in the race to
find substance X, is that correct?

7

8

A. That's correct.

9

Q. But as yet, as I understand it,
no one has done that using HPLC?

10

11

A. At the present time no one has
done that.

12

13

14

15

16

Q. So at least presently using the
HPLC method as it has been used, we have heard from
Mr. Cimbura, it has not been possible to separate
out substance X from digoxin because we haven't gone
through the procedure that you have described?

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DP.jc
D

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A. Well, to my knowledge no one has - there are some studies, I must retake on this - there are some studies that I have heard coming out from Dr. John Gault's laboratory.

Q. John who?

A. Gault.

Q. And that is G-a-l-t?

A. G-a-u-l-t, in Newfoundland in which I have been led to believe he has managed to separate, by HPLC, digoxin from another compound. This is hearsay, I have not spoken to Dr. Gault myself on that particular issue.

Q. Do you know what the other compound is?

A. No.

Q. Once you had gone through this procedure of yours that you have described, would it then be possible to develop a standard for Substance X that could be routinely run through HPLC?

A. If we could identify its structure and if we could then purify it we would have a standard which could then be used.

Q. That would make the detection - excuse me, the separation of digoxin using HPLC considerably more reliable?



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A. Well, you would then be able to identify where it ran chromatographically. Did it run with digoxin? You would be able to attempt to separate the two.

Q. With some considerably more precision than would be possible at present?

A. It would be a lot easier, yes, if you had a standard.

Q. Now, I do not want to spend a great deal of time on this, but since we are speaking of methodologies for the detection of digoxin, if you can look again at the last page of Exhibit 25 there is also reference to an EIA in the bottom left-hand corner which I gather is enzyme immunoassay?

A. Enzyme immunoassay, yes.

Q. Is that a similar procedure to RIA, in general terms?

A. It is somewhat different. It also has antibody reactions.

Q. And then at the bottom there is FIA. What is that?

A. Fluorescence immunoassay, and it is again similar, but also has some antibody involvement.

Q. Just out of interest, that



D.3

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procedure seemed to produce the least deviations.

3

Is there anything about that system that makes it

4

very specific or very accurate?

5

A. It is probably - I have never

6

used the FIA procedure for digoxin and it does appear

7

in this particular month's report to have performed

8

rather well.

9

Q. And speaking of performance,

10

am I right that where it says in this report, near

11

the bottom, two-thirds of the way down the page,

12

your result was 3.5. Is that the Hospital for Sick
Children?

13

A. On that particular month, yes.

14

Q. Using which, FPIA or --

15

A. RIA. We have not yet switched

16

we are not one of the 35 labs reporting the FPIA

17

in that month.

18

Q. You have mentioned in your

19

evidence, both today and yesterday, that mass

20

spectrometry is one method that you would consider

21

highly reliable for the detection of digoxin
concentrations?

22

A. Yes.

23

Q. My understanding of that method

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is that it is certainly not one that you would use

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in a therapeutic context, on a regular basis at least?

A. That is correct. It requires very expensive equipment. The combination of a liquid chromatograph and a mass spectrometer, you are talking of something around \$350,000 and you could only measure a few samples a day.

A routine laboratory gets 20 or 30 samples every day for digoxin, at least ours does, and you could not possibly apply that method to all the samples we get.

Q. I gather that mass spectrometry is a method that uses the - I am going to put this badly because I am going to try to put it in very simple terms, but it works on the molecular weight of substances?

A. Mass spectrometry?

Q. Yes.

A. What happens is, the molecules get broken down and the fragments can then be identified. Digoxin will break down very characteristically. There is a characteristic breakdown pattern for every compound that exists and therefore you can identify - fingerprint that molecule with a mass spectrometer, very specifically.

Q. And you feel, using a mass



D.5

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spectrometer, that you could separate digoxin from
Substance X?

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A. I have not done that, but I feel
that that is probably the route. It may not
separate chromatographically but even if it does
not separate chromatographically one will be able to
subtract the digoxin spectrum from Substance X
spectrum and therefore identify Substance X.

9

10

Q. Are you in the race for the
identification of Substance X?

11

12

13

A. I am interested in identifying
Substance X, yes. I do not know that I am in a race.
I am interested in identifying this compound.

14

Q. Are you looking for funding to
finance it?

15

16

A. We would like funding, yes.

MR. STRATHY: Perhaps you could speak
to the Commissioner.

17

18

THE COMMISSIONER: I am already in
trouble.

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MR. STRATHY: Q. Doctor, let me ask
you some questions for a moment about your method-
ology, and I recall from your evidence yesterday that
all the sampling that you are talking about that you
did was with respect to blood, whether it be plasma
or serum. Is that right?



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A. That is right.

Q. And that blood is what you use in your day-to-day monitoring in the Hospital?

A. For most drugs. Occasionally we would use saliva but for most drugs we use blood, yes.

Q. Again, all the work that you did, at least as a routine basis, was on samples from living children and not as a routine matter, certainly, on post mortem samples?

A. The Hospital has an instruction that all autopsy samples are analyzed on a routine basis, so I would have to say we do routine ante mortem, of course; we are compelled to do routine autopsy monitoring.

Q. You say compelled. I take it that is not something then that you really consider to be your bailiwick as a clinical biochemist?

A. I think I would prefer not to be doing that.

Q. Is there some reason for that?

A. Well, I am trained in several areas. One is as a clinical biochemist and that means that I am interested in patient care. Once the patient dies there is nothing I can do for that



D.7

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particular patient. I think samples should then probably be sent to forensic laboratories at that point in time.

Q The procedures that you have mentioned you use on living patients, you have indicated were specifically designed and intended for use in just that setting, the clinical therapeutic setting. Do you have any reservations about using those methodologies on the post mortem samples that are provided to you in the autopsy context?

A Well, I would have the reservations that any scientist would have who has read the data that we are aware of, that is, does Substance X, if we call it that, if released after death would it contribute to the possible measurement by either RIA or FPIA or whatever procedure?

In order to answer those questions, one really has to develop this mass spec method and we can then address that issue, but until we know what we are measuring in post mortem samples we cannot address that issue.

Q That, it seems to me, is a very critical point that you have raised, and I gather from what you are saying that you cannot say,



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at this point in time at least, whether Substance X is in fact released post mortem, on the basis of the current scientific knowledge about it?

A. I can only share my experience with you. We have measured a digoxinlike compound, whether it be Substance X or whatever, in some autopsy samples, in patients that were never receiving digoxin.

THE COMMISSIONER: In patients who were never receiving --

THE WITNESS: In patients who were never receiving digoxin.

MR. STRATHY: Q. So --

A. At least according to the medical records.

Q. Are those patients in the category that we have been talking about previously, that is, less than three months of age?

A. No, some of them are older. In fact, the highest reading was obtained in a close to five year old infant.

Q. The evidence we have heard, I believe so far, is that Dr. Seccombe's findings of Substance X were zero, after three months of age?

A. He did not look at post mortem samples, I don't think.



D.9

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Q No, you are quite right. So we know from Dr. Seccombe that it may exist pre-mortem up to three months of age. What you are telling us is that your studies show that it may exist post mortem in other children?

A. Correct.

Q Even older than three months of age?

A. Right.

Q How many children did you test, post mortem?

A. We have done a lot of autopsy samples and, again, I would prefer the autopsy data to be handled by Dr. Phillips, but I can share some of our experience with you.

The total number of post mortem digoxins that we have done at the Hospital between March 24, 1981 and April 24, 1983 is 520, and during that time period there were nine patients that we are aware of that had never received digoxin and that had measurable digoxin concentrations, using the RIA technology. The highest result was 2.1 nanograms per millilitre, in that particular series.

Q That is in serum, is it?

A. In serum or plasma, yes.



D.10

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Q. Are you able to give us any
breakdown in terms of the ages of those nine patients?

A. I have it here, yes. I would
be quite happy to make this document available to
you, should you so wish.

MR. STRATHY: I wonder, Mr. Commissioner,
if I could just see it for a moment. Do you mind if
I just confer with the witness for a moment to try
to understand some of this, as it were, off the
record?

THE COMMISSIONER: It is a bad habit
to get into, but --

MR. STRATHY: I will put it on the
record.

THE COMMISSIONER: Yes, all right.

MR. STRATHY: Q. Do I understand it,
Doctor, that these nine that we have here are the
nine children who had not been receiving digoxin, in
which you detected digoxin levels at post mortem?

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E/BB/ak

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A. That is correct. I was given this list by Dr. Phillips. This isn't my list, I haven't compiled it, Dr. Phillips has.

Q. All right, before we go any further then, do I understand, Mr. Lamak, perhaps you can help me, Dr. Phillips will be called and that the other data that accompanied this list will be introduced at some point?

MS. CRONK: Yes, Mr. Commissioner, we have already indicated that we will call Dr. Phillips when available to testify as to the autopsy results including, as I understand it, these nine children.

THE COMMISSIONER: All right.

MR. STRATHY: Thank you very much, Miss Cronk. I do propose that this be made an exhibit but if I can first just take you through it briefly, Doctor. It indicates, it seems to me, that in the nine children that fell in that category, there were ranges observed between 1.0 nanograms per millilitre and 2.1 nanograms per millilitre.

THE WITNESS: That is right.

MR. STRATHY: Q. And the age of the 2.1 nanograms per millilitre was approximately five years, as you have already indicated.



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A. Right.

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Q. And the ages seem to range

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between virtually new born to five years of age.

5

A. Yes.

6

Q. It appears that in at least six

7

of the cases, the children had been on Ward 7G.

8

What is 7G?

9

A. It is our Neonatal Ward.

10

Q. I'm sorry?

11

A. Our Neonatal Ward.

12

Q. All right. May this be

entered as the next exhibit?

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THE COMMISSIONER: Exhibit No. 27.

14

---EXHIBIT NO. 27: Chart - re Age of Nine
Children.

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THE COMMISSIONER: You don't mind

parting with this, or do you?

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THE WITNESS: If I can get a copy

back.

20

THE COMMISSIONER: Yes, all right.

21

Well, I think we can probably get copies back.

22

May I just ask this one question.

23

Neonatal doesn't mean premature, it means just

24

close to birth, is that right?

25

E2



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THE WITNESS: Right.

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MR. STRATHY: Q. I take it that

4

you're not able to tell us with respect to these

5

nine children whether these levels existed pre-mortem?

6

A. No.

7

Q. So, really, what you are telling

8

us is that based on your research there is a possi-

9

bility at least that substance X is released post

mortem?

10

A. There's a possibility, yes.

11

Q. And this is something I take it

12

you want to pursue further as well?

13

A. Yes.

14

THE COMMISSIONER: Unless of course

15

it is digoxin that's released post mortem?

16

THE WITNESS: None of these children

were known to be on digoxin.

17

THE COMMISSIONER: No, no, but it's

18

a substance that's released.

19

THE WITNESS: Unless there is

20

endogenous digoxin.

21

THE COMMISSIONER: The substance

22

could be digoxin, couldn't it?

23

THE WITNESS: Could be, yes.

24

MR. STRATHY: Q. I suppose the

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other possibility too is that for some reason they
were administered digoxin and it wasn't recorded?

3

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A. That's the other possibility.

5

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Q. All right. These samples that
were taken with respect to the nine children we've
just mentioned, were they taken within a reasonably
short time after death? Do you know when they were
taken?

7

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A. I don't have the times. I don't
know if they're on that, time of sampling relative
to time of death. I'm not aware of that.
Dr. Phillips would have that.

11

12

13

Q. So, you don't know when the
samples were taken?

14

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A. Unless it's on that list, I
don't know.

16

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THE COMMISSIONER: I don't see it
on here.

18

19

THE WITNESS: But Dr. Phillips
would have that data.

20

21

THE COMMISSIONER: I don't see
anything there that would be of any help.

22

23

THE WITNESS: It's not on there.

24

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MR. STRATHY: Q. Can you tell us
as a routine matter when would an autopsy blood



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sample be taken?

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A. Well, it would be variable.

4

It depends on the length of time it perhaps takes

5

to get parent consent. It might be a few hours to...

6

Q. Let me ask you this, Doctor.

7

We have heard in previous evidence that with respect

8

to blood serum levels, there is what has been

9

described as a multiplier effect between pre-mortem

10

and post mortem levels. Is there, in your view,

11

a possibility that this same multiplier effect may

12

A. It's a hypothetical. It may

13

occur.

14

Q. It's a possibility though?

15

A. It's a possibility.

16

THE COMMISSIONER: Probably we've

17

had this, but these were autopsy babies that you

18

were examining for digoxin, is that right?

19

THE WITNESS: Yes.

20

THE COMMISSIONER: But I understood

21

an autopsy of course will only be - it is only rare

22

occasions that there will be an autopsy. There's not

23

an autopsy automatically on the death of a baby, is

24

there?

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THE WITNESS: No, there isn't,



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you're right.

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THE COMMISSIONER: There is?

4

THE WITNESS: No, there isn't.

5

THE COMMISSIONER: There isn't.

6

THE WITNESS: Right.

7

THE COMMISSIONER: Well, did I
not understand that as a routine the Hospital had
tested all babies who died for digoxin?

8

9

THE WITNESS: Well, certainly all
autopsy ---

10

11

THE COMMISSIONER: Which is the
right pronunciation, autopsy or autopsy, or had I
better look it up?

12

13

14

THE WITNESS: Well, ---

15

THE COMMISSIONER: Well, autopsy,
that's your pronunciation, and you are a lot more
familiar with it than I am, but it is not true then
that the Hospital had all babies who died from
March of 1981 on tested for digoxin?

16

17

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19

THE WITNESS: There are people
that could answer that question better than I can.

20

21

THE COMMISSIONER: Well, would the
500 that you mentioned, you said you did 520, that
is 520 tests that you did and there may have been
fewer than 520 autopsies? Is that right?

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Soldin, cr.ex.
(Strathy)

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THE WITNESS: Well, in fact, on this list that Dr. Phillips gave me, this is another list that you don't have yet, the total number of post mortem examinations during that same period was 705. So, not every post mortem examination had a digoxin analysis done over that period.

8

THE COMMISSIONER: Well, some day we'll get that cleared up.

9

10

11

MR. STRATHY: It sounds as though it's going to come in through Dr. Phillips, so, perhaps we can defer.

12

13

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Q. Just one point of clarification on that subject though, Doctor. In your testing of these samples, did you have some instances where children who had not been administered digoxin had no concentrations of digoxin detected?

17

A. Oh, most definitely.

18

19

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Q. All right.

A. So, in many cases, there was no record of digoxin and the results obtained was less than 0.5 nanograms per millilitre.

21

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Q. And I take it in a number of other cases you had children who had been receiving digoxin and therefore you did detect digoxin levels in those children?



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A. Right.

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Q. And all the results are
available in some published form of which the
last exhibit is just a part?

6

7

A. And if they're not Dr. Phillips
I'm sure can make them available.

8

9

Q. All right, thank you. So, there
is some body of data somewhere?

10

11

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A. There is, yes.

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Q. I think we got into this area when
I was asking you about your work on blood and I
just want to be sure, I think you confirmed it
already, that none of your work, whether it was
pre-mortem or post mortem was with respect to
tissue.

A. Yes.

22

23

24

25

Q. And would you agree with the
evidence of Dr. Ellis that one could develop a
method for using RIA on tissue but it would take
some months at least to develop it?

A. It would take a time period of
several months, yes.

26

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Q. I'd like to turn to a different
area, and perhaps you could have Exhibits 15B and C
placed in front of you and also perhaps Exhibit 24;



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24, 15B and C.

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A. Right.

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Q. And one of the either two or
three in Ontario that have that sort of program?

12

13

A. I'm not aware of any other
hospital in Ontario that has this.

14

15

Q. I'm sorry. So, as far as you
know, you are the only hospital in Ontario?

16

A. Right.

17

18

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Q. Now, you testified yesterday
that the therapeutic levels for digoxin are, in your
view, 0.8 nanograms per millilitre to 2.0 nanograms
per millilitre?

20

21

A. Those are the concentrations of
digoxin that are probably therapeutic.

22

23

Q. As opposed to probably sub-
therapeutic and probably toxic, is that right?

24

A. Yes.

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Q. And if you look at the back of
Exhibit 15B, at the very bottom, it says:

4

"General guidelines for therapeutic
drug monitoring."

5

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THE COMMISSIONER: Where do you see
that?

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8

MR. STRATHY: It's the back of
Exhibit 15B.

9

10

THE COMMISSIONER: It's not on the
back of mine.

11

12

MR. STRATHY: Well, maybe you only
got the front copy, sir.

13

14

THE COMMISSIONER: I see. Well,
perhaps the back has a second page.

15

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MR. STRATHY: It could be. It is
I believe on the form itself, it is on the back.

17

18

THE COMMISSIONER: Yes, all right.
What does it say, I'm sorry?

19

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MR. STRATHY: At the very bottom.

21

22

THE COMMISSIONER: "Some patients
may require a more individualized
approach."?

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MR. STRATHY: No, just the one
above that where it says "Digoxin", and there it
shows the level in the column that called "Therapeutic



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Range", it shows a level of .8 to 2.0.

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Q. I understand that that letter is
a Greek letter mu, is it?

5

A. Right.

6

Q. And that stands for micrograms?

7

A. Right.

8

Q. Micrograms per litre translates
to nanograms per millilitre?

9

A. Correct.

10

THE COMMISSIONER: Not dead on.

11

MR. STRATHY: I beg your pardon?

12

THE COMMISSIONER: Not dead on.

13

MR. STRATHY: Well, as I understand
it, it does. Where we get into trouble is with
moles.

15

THE WITNESS: It translates exactly.

16

THE COMMISSIONER: Oh, I see, all

17

right.

18

MR. STRATHY: Since there are

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1,000 millilitres in a litre and 1,000 nanograms in
microgram, it's the same.

20

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THE WITNESS: Yes.

22

MR. STRATHY: Q. So, is that what
you had in mind when you gave us those figures of
.8 to 2, is that the reference?

23

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A. Yes, that's the reference.

3

Q. And the same appears on Exhibit

4

24, which you don't need to put in front of you,

5

but it is the TDX data sheet on digoxin, I believe

6

it specifies the same range.

7

THE COMMISSIONER: You say Exhibit 24?

8

MR. STRATHY: Q. Exhibit 24. Do you

9

have that in front of you, Doctor?

10

A. Yes, I do.

11

Q. I believe that level is set out

12

in that exhibit. I'm just trying to find the
reference.

13

A. It's on page 17.8.

14

Q. Page 17.8, the top paragraph

15

where it says "Expected Results". It says:

16

"Optimum therapeutic level affects

17

are usually observed when serum levels

18

are in the range from 0.8 nanograms

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per millilitre to 2.0."

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A. Right.

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F/DM
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Q. Is this document,
Exhibit 24, the source document for the
references?

A. No, no. Document 24
didn't exist when these requisitions were styled
and developed. We had, and I had many discussions
with the clinical pharmacology group at Sick
Children's and it was their experience, as well as
some, many papers in the literature, that this
would be an appropriate therapeutic range. The
American Association for Clinical Therapeutic
Drug Monitoring Program, in fact, recommends
that range and they have published a little
booklet which I have here which provides that
range, this was one of the source documents.

Q. So were you one of the
people responsible for the preparation of
Exhibit 15-B?

A. Yes.

Q. And it was as a result of
these discussions and references that you have
referred to that this particular range was
picked?

A. Right.

Q. And that seems to be the



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range that is recognized at least by the community of which you are a member?

A. Correct.

Q. Is that a range specifically designed at the Hospital for Infants?

A. It is the general range applying to infants and children at our institution.

Q. Is there a difference between the general range for infants and children and the general range for adults?

A. We don't employ a difference. There is a range for probably therapeutic concentration of digoxin is the same in our institution as it is in many adult institutions.

Q. We have had entered in evidence already and marked as Exhibit, I am not sure now, Exhibit 11, I don't recollect exhibit it was, but it was the reference to the Residents' Handbook.

MS. CRONK: Exhibit 16.

Q. Exhibit 16, Page 365 of the Handbook.

A. Yes.

Q. Now, as you see under reference values there is a reference, the optimal



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range being 0.5 to 2.5 nanograms per milliliter.

A. Yes.

Q. All I want to ask you is this.

Do the figures that we see on Exhibit 15, the
therapeutic drug monitoring program figures ---

A. Yes.

Q. Do they represent a reduction
in the hospital's view of what the therapeutic
range is?

A. They are somewhat a reduction,
they were developed by different people. They were
arrived at by different groups. I should point out
something perhaps that you are not aware of, and that
is that every patient report that emanates from the
drug monitoring laboratory is a computerized
cumulative report which has on it the therapeutic
range of the drug that has been requested.
So if a request has been made for digoxin analysis,
the report will carry with the actual result the
therapeutic range for digoxin at 0.8 to 2.0.

Q. That is something that has
recently ---

A. That has been for at least
a year that we have been computerized, yes.



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Q. I just wanted to be clear
on this and I take it you are agreeing with me that
between the time that this handbook was published,
the 6th edition in 1979 and 1982 or 1983, there
has been a downward change in the therapeutic
range that the Hospital recognizes.

THE COMMISSIONER: It is downward
and upward, isn't it?

A. It is upward at the moment.

Q. It is upward at the bottom
and downward at the top.

A. Yes.

THE COMMISSIONER: Thank you.

Q. It is revised upward at the
bottom and downward at the top.

A. Right.

Q. Now, Exhibit 15-B and C
also referred in the last column, "Interacting
Drugs."

A. Yes.

Q. To the interaction between
digoxin and quinadine.

A. Yes.

Q. And I gather, again, looking
at your resume and without going through the



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references themselves, that the interaction of various drugs is something with which you have had some both practical and academic experience.

A. Yes.

Q. In fact, you have written a paper and I think delivered a presentation -- I am sorry, written a paper on the interaction of digoxin with co-administered drugs.

A. Correct. I am one of the co-authors of that.

Q. And you have also written another paper about the interaction of digoxin and verapamil.

A. Correct.

Q. And I would assume again that the cross reactivity between drugs is something that is very important to know about in a clinical setting.

A. Right.

Q. Not only so that you can know exactly what it is that you are analyzing, but also so that you can interpret the findings that you make so that you can treat the patient properly.

A. Yes.



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Q. Now, Dr. Ellis, I believe, testified that in his view there were two types of interaction, one which he called an analytical interaction; and another which he called a therapeutic interaction, do you recall his evidence?

A. Yes, I think he explained it very well, yes.

Q. So I take it you agree with his characterization.

A. Yes.

Q. Which is quinidine, is it the kind that shows up analytically as digoxin or is it what I call the booster that boosts the digoxin level?

A. It boosts the digoxin level, it is not an analytical problem.

Q. So that in any particular infant receiving digoxin and quinidine at the same time is there a possibility that quinidine will have the effect of actually raising digoxin levels?

A. That is correct, yes.
If you have a steady state concentration of, let us say, one nanogram per milliliter of digoxin and then quinidine is added to the patient's drug regimen, you could anticipate that the digoxin



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concentration will increase.

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Q. Are you able to assist us
at all as to how much it would increase?

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A. I think they are variable,
but it could double quite easily.

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Q. Could it go higher than
double?

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A. Possibly, yes.

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Q. Now, on Exhibit 24 which I
think you still have in front of you, the TDX
information, Page 17.4 of that.

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A. Yes.

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Q. That shows the interaction
between digoxin, the assay, and various other drugs.
In the very beginning of the left hand column it
mentions digoxigenin 205%. I gather digoxigenin
is one in the first category of interactivity that
is the analytical interaction, is that it?

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A. Yes.

19

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Q. Do I read that correctly as
saying that the assay would measure that
particular compound and the results shown would be
approximately double?

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A. That is my understanding, yes.



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Q. Now, I just wanted to be sure so that if there is one nanogram of digoxigenin per milliliter in the serum being measured it would in fact show up as two nanograms?

A. It could show up as 2.05 nanograms per milliliter, it would show up as.

Q. Then at the top of the next column is a reference to digitoxin and, again, we have heard that digitoxin creates the same analytical problem.

A. Yes.

Q. But I had been led to understand that the effect of measuring digitoxin was that digitoxin would read on the assay at a higher basis than was actually in the serum.

A. Well, it has 3.6 cross-reactivity, according to this.

Q. Would that not mean that if you had 100 nanograms per milliliter of digitoxin in the serum you would only get a reading of 3.6?

A. I think the best interpretation is given on the page before that, so if you would just go to the page before that, which defines the percent cross-reactivity is equal to 100 times the measured



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1 digoxin concentration divided by the concentration
2 of the cross reactant. Now, all one has to do is
3 put in the knowns and you can determine what the
4 measured digoxin concentration would be for any
5 of these compounds listed. You have a very simple
6 equation there and the only unknown is the measured
7 digoxin concentration.

8 Q. Yes.

9 A. And by applying that formula
10 you will arrive at the cross-reactivity for the
11 concentration of digoxin that -- that that
12 particular compound would produce. For example, if
13 we took progesterone because it is simple, because
14 they are using figures of 10 milligrams per milli-
15 liter which has a cross-reactivity of .01 percent,
16 and if we apply that formula, then it would be that
17 .01 is equal to 100 times the measured digoxin
18 concentration divided by the concentration of the
19 cross reactant which in this case is 10 micrograms,
20 or 10,000 nanograms. We have to convert to nanograms
21 because we have to use the same units. If we did
22 that little mathematical calculation it would work
23 out that progesterone at a concentration of 10
24 micrograms per ml would read a digoxin concentration
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of 1 nanogram per ml.

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Q. So that the effect of all these things is that they will give a reading of digoxin in response to an actual concentration of the substance shown in the left hand column.

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A. Yes.

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A. Right.

Q. Given what you have told us about cross-reactivity, both your experience with it and the importance of it in a clinical setting, I take it that this sort of information is not only of significance to you but also exactly what you would expect to receive from a manufacturer of a particular assay.

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A. It is what we would hope to receive, yes.

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Q. It is pretty standard, I would think, in the industry.

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A. It should be.

Q. Well, I asked Dr. Ellis last day about the problems at Antibodies Inc. and the



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fact that he had not been able to get information from them. I suggested to him that seemed incredible they couldn't provide that information. Does it strike you as incredible that the information isn't there?

A. It is disappointing, yes.

Q. Surprising?

A. Surprising.

Q. On Exhibit 24 at the very beginning, the paragraph entitled "Intended Use" and about eight lines down, seven lines down, it says:

"Digoxin intoxication is a common and serious problem in the clinical setting."

And I believe you were here for Dr. Ellis' evidence when I asked him whether he was familiar with the literature in that regard. Are you familiar with literature to the effect that digoxin intoxication is a common problem?

A. Yes.

Q. Are you familiar with ranges suggested in the literature? I have seen references to anywhere from 10% to 30% of adult



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patients being treated with digoxin.

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A. I think that is quite a high percentage in the ranges you are quoting. The diagnosis of digoxin toxicity is a clinical one as Dr. Ellis mentioned. The therapeutic monitoring laboratory would provide an indication that the drug concentrations are now approaching possible toxic concentrations. The Commission should, therefore, evaluate closely whether or not toxicity exists.

Q. Well, we know from what you have already said that your responsibility is not to do that clinical evaluation of toxicity.

A. Correct.

Q. But you can certainly speak for what you see in terms of the results you observe, and I am going to ask you, based on your observations at the Hospital for Sick Children, do they confirm that in the children being treated with digoxin, intoxication is a common phenomena, according to the levels that you consider to be toxic?

A. It occurs fairly frequently.



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Q. Can you give us any assistance
as to what the degree of frequency is?

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A. I think you will get a better
percentage from a cardiologist.

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Q. That is a fair statement, but
I have a biochemist at the moment and I would
appreciate knowing what you see in terms of your
results?

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A. But I don't see clinical
toxicity; I see a digoxin concentration that may be
over 2.

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Q. That is what I am asking you
about.

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A. We can check that up. A
significant number of the results that we measure
are over 2. If you ask me for percentage, just with-
out checking up, I would say somewhere between
10 per cent and 20 per cent probably.

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MR. STRATHY: Thank you very much,
that is fair.

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I will undertake, Mr. Commissioner,
for the witness at least, to refer him to the studies
that I have mentioned as to the toxicity levels in
adults.

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THE COMMISSIONER: That is fine.



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MR. STRATHY: Q. If you could look at page 17.7, there is just one last matter on that exhibit that I would like to clarify. In the paragraph "Limitations of Procedure" --

A. Yes.

Q. It says, in the last sentence of the first paragraph, it says:

"Samples from patients receiving digitoxin or crude digitalis therapy will show falsely-elevated values for digoxin."

Now that is where I have trouble, because if you look at Table 1 which is the table of cross-reactivity, it does not suggest that digitoxin has such a high cross-reactivity, but I read the paragraph on 17.7 to say that if you use the test on digitoxin patients you will get values that are falsely elevated.

Can you help us with that?

A. That is a statement that they have made, and if you calculate from Table 1 on page 17.4 you can work out what the cross-reactivity would be, using the same formula we discussed. It would not be that much of an elevation, if you put these numbers into that formula.



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Q. Whatever it is, it is clear I suppose that if you were to try to measure digitoxin you should not be using this assay?

A. No, the antibody is not for digitoxin, but it is for digoxin. Digitoxin cross-reacts to a small extent.

Q. The most recent exhibit - or one of the most recent - was Exhibit 26, your slides. Looking at page 6, which is the second of two pages, you took us through the diagram on the left hand side and you mentioned an initial factor, patient compliance, that is whether the patient does or does not swallow his pill. Judging from your Form 15B and 15C that is a concern sometimes I suppose, particularly in children, that they do not take the pill that they have been given, or swallow the syrup, or what have you.

A. It could be a concern, yes.

Q. The next thing on that form is medication errors and I take it as given that medication errors are something that happen from time to time in hospitals. As long as there are human beings running hospitals there will be medication errors.

A. Right.



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Q. And we know in point of fact that on Ward 7F there was a medication error with respect to epinephrine and Vitamin E?

A. Yes.

Q. Which resulted in sickness in a number of children?

A. Yes.

Q. And I gather from what you are saying, from what you said in your evidence in chief, that with respect to the one child where there was a level of 1.3 digoxin, on Ward 7F, do you recall your evidence about that?

A. Right.

Q. That there is at least a possibility, and I put no higher than a possibility, that there was a medication error in respect to that child.

A. It is possible. That was the conclusion, I think, in the Dubin Report.

Q. The other possibility, to paint the whole picture, is that it was substance X and not digoxin?

A. Right.

Q. Do you, as a matter of your routine work at the Hospital, become involved in the



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analysis of samples in respect of which there have been medication errors?

A. Occasionally, yes.

Q. Is that something which you monitor, in a sense, medication errors?

A. If one takes the 7F situation, these children became very ill. We did not know why they became ill. Because of the Hospital's history with digoxin we ended up doing a number of assays for digoxin.

Q. That was after the recognition that there was or might be a problem. My question is, as a routine matter, are you watchdogs for medication errors?

A. Certainly in the drug monitoring area, yes.

Q. And drug monitoring in a sense of both before and since the Therapeutic Drug Monitoring Program?

A. Yes.

Q. And you are using drug monitoring not as a label for the particular program that you have introduced recently but for the process that you are engaged in and have been engaged in while you have been at the Hospital?

A. Yes.



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Q. When a medication error takes place, is there some sort of a report that is prepared?

A. You would have to ask the clinicians running the wards. We would report everything that our laboratory does. It is then in collaboration with the clinicians. In the 7F situation, the infants became very ill and a lot of additional tests were done, not just digoxin.

Q. Let me be more specific. In your between monitoring, if you detect something which appears to reflect a medication error, does your laboratory prepare some sort of a report?

A. No report other than the normal report. What we would do is relay our findings. Let us say a patient was given an inadvertent amount of another drug, let us say, theophylline or phenytoin, we then measured the concentration of this drug, found it to be extremely high, so the clinicians on the ward as well as the clinical pharmacology unit as well as - well, these two areas would be contacted immediately. In fact, it is routine practice whenever we have a concentration over a particular level, over a particular value, to immediately phone the ward as well the



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clinical pharmacology division.

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Q. Let me just try and hone down
my question a little.

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First of all, I gather there would
be several potential types of medication errors.

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You might have, firstly, a child given too much

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of a drug which had been prescribed for him or her.

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That is one type of error that could happen, is it
not?

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A. Yes.

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Q. If you are monitoring that drug
that would be something that would hopefully show up
in your monitoring?

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A. Yes.

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Q. You would detect higher
concentrations than should be there?

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A. Yes.

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Q. And you would report that to
the ward?

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A. Immediately, and to the
clinical pharmacology division.

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Q. Another type of error that could
happen is that a child could be given a drug that
was not prescribed at all for him, or her?

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A. Right.

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Q. Is that something that would be detected in your monitoring?

A. That is almost impossible to track down. It is very difficult, as the 7F situation showed. Children were given a drug which was not prescribed. It took many weeks to track that down.

Q. So in the clinical monitoring that you do, you are only monitoring things that are expected to be found in the child?

A. Yes.

Q. Let me ask you this. When you do detect that there are excessive concentrations of a drug that has been prescribed for the child, you say that you notify the ward and you notify the clinical ---

A. Pharmacology Division, yes.

Q. Do you do that - is there any report that you do to them or ---

A. Well, there is immediate notification by telephone that the results are abnormally high in such and such a patient for such and such a drug.

Apart from that, there is the usual reporting system which is that at 1600 hours every day



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2 the results are reported to the wards on all the
3 analyses which we perform. At 1600 hours we also
4 print out what is known as an Exception Limit
5 Report Form. This Exception Limit Report Form
6 reports all the concentrations measured during that
7 day which were very sub-therapeutic or toxic, and a
8 copy of that computer printout is given to the
9 Clinical Pharmacology Service at 1600 hours as well
10 as to the Microbiology Service and Infectious Disease
11 Service.

11 Q. Let me ask you one final
12 question.

13 In your experience prior to March of
14 1981, in the therapeutic monitoring of digoxin, had
15 you encountered instances which appeared to reflect
16 medication errors in the administration of digoxin?

17 A. Prior to March 1981 I was
18 not responsible for digoxin analyses.

19 Q. That is probably the best answer
20 you could have given me. Are you able to assist us
21 in that at all? I suppose you cannot?

22 A. I was not responsible for it,
23 unless Dr. Ellis would have brought it to my attention.

24 Q. How long is it that you have
25 been responsible now for digoxin monitoring?



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A. Since July of 1981.

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Q. Let me ask you, in that period,
Doctor, had there been instances which appear to
reflect medication errors or errors in the administra-
tion of digoxin?

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A. Not to my knowledge. There is
no doubt we get children that develop toxic concentra-
tions of digoxin. They need alterations in the drug
regimen. It is not a medication error.

Q. Can you go as far as to say
this, that you have observed toxic levels which
you cannot necessarily say why they are toxic? All
it is is that you have observed toxic levels.



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A. One observes toxic levels because of the individual difference in drug disposition. As I explained yesterday, you cannot predict a serum concentration for any given dose. So, you've got to try a dose, a recommended dose and then you have to follow that up by measuring the serum concentration.

Q. Well, have you observed levels in that time period that you've mentioned since you started doing it, that were sufficiently high that they might reflect the medication error?

A. We've observed levels. I think the highest level we have observed in the routine monitoring is probably around 14.

Q. 14?

A. 14 nanograms per millilitre.

Q. And is that a level that ---

A. Well, that child actually got into some digoxin tablets of its parents. So, it was a toxic overdose situation.

Q. That's not therapeutic monitoring?

A. No, but we were involved. We have observed levels between 5 and 10 occasionally; not too frequently but occasionally. The decision



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as to whether that is due to a medication error, I would advise you to ask Dr. Speilberg and Dr. MacLeod, the Clinical Pharmacology people.

Q All right. So that is really not something that you are able to comment on?

A No.

Q All right, thank you, Doctor. Those are my questions.

THE COMMISSIONER: I think we'll probably rise now but I might get some indication as to timing. Mr. Hunt, have you any thoughts on how long you will be?

MR. HUNT: 15 minutes.

THE COMMISSIONER: You are next, Mr. Shinehoft?

MR. SHINEHOFT: I don't have any questions.

THE COMMISSIONER: Ms. Jackman?

MS. JACKMAN: Unless my questions are asked, I only have about five minutes.

THE COMMISSIONER: Five minutes. Miss Kitley?

MS. KITELY: 10 or 15 minutes at the outside, Mr. Chairman.

THE COMMISSIONER: Mr. Young?



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MR. YOUNG: I have no questions,
Mr. Commissioner.

THE COMMISSIONER: Mr. Ortved?

MR. ORTVED: I have no questions at
the moment.

THE COMMISSIONER: Mr. Olah?

MR. OLAH: Well ---

THE COMMISSIONER: No, I'm not, I just
want to know how long you will be?

MR. OLAH: Mr. Commissioner, the
problem I've got, as you may have seen, I was away
for part of the morning and I would like to verify
that some of the questions I have have not already
been asked, so, I can't be precise. But certainly
I will be short.

THE COMMISSIONER: All right.

Mr. Tobias?

MR. TOBIAS: 15 minutes, Mr. Commissioner.

THE COMMISSIONER: Mr. Labow?

MR. LABOW: No questions at the moment,
Mr. Commissioner.

THE COMMISSIONER: Mr. Roland? I take
it you want to be last?

MR. ROLAND: Yes, I would like to be
last and I do have one or two questions at the moment



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and I may have more, depending on other questions

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asked. Thank you.

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THE COMMISSIONER: Well, that - you
may have some re-examination in any event.

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MS. CRONK: Yes, I anticipate some
questions.

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THE COMMISSIONER: Well, I don't think
there is any need to make any special arrangements.

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I think we will just carry on until one o'clock and
see what the situation is then, but it does not look

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as though we will certainly not get to another

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witness that we can complete.

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MS. CRONK: Thank you.

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THE COMMISSIONER: Yes, all right.

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Oh, sir, where is Miss. Solomon?

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MS. SOLOMON: Here.

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THE COMMISSIONER: Oh, yes, sorry, I
missed you. Did you have any questions?

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MS. SOLOMON: I have no questions.

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THE COMMISSIONER: No, all right,
thank you.

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--- Short recess

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--- Upon resuming:

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THE COMMISSIONER: We'll try again,
Mr. Hunt.

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MR. HUNT: Thank you, sir.

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CROSS-EXAMINATION BY MR. HUNT:

Q. Dr. Soldin, with respect to the FPIA method, I take it that you have given really two guarded conclusions at this point in your experience with it; that is, one, that it is more specific than RIA and, two, that it gives generally lower readings than the RIA method?

A. Lower readings in patients not on digoxin, not known to be on digoxin. Those are guarded conclusions, yes.

Q. And with respect to the post mortem samples.

THE COMMISSIONER: I am sorry, I didn't get the answer. Did you agree with that leading question, that it is more specific and it is lower than RIA?

THE WITNESS: I'm saying it could be more specific, yes. Our findings at the present time would indicate that it probably is.

THE COMMISSIONER: And what about being lower?

THE WITNESS: Lower, generally our findings are on the average in patients that are not receiving digoxin, that is, we have done some studies on the neonates not on digoxin, as well as on the



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autopsy samples, in those two areas.

MS. CRONK: Excuse me, Mr. Commissioner,
I too am having difficulty hearing the witness.

THE WITNESS: I'm sorry, in those two
areas the results by FPIA tend to be lower than the
results by RIA.

MR. HUNT: Q. So, with respect to the
post mortem samples that were analyzed, am I correct
that in 23 of the 36 cases, the results were
negative, that is, they were lower than .5.

A. In 23, yes, they were lower than
.5 in what I would call Group 1, 23 of that.

Q. All right. And that in nine
cases the RIA analysis gave a reading that was higher
than the FPIA analysis?

A. That's correct.

Q. And in two cases ---

A. That would be Group 3.

Q. All right. We're still dealing
with the 36 post mortem samples?

A. 37.

Q. 37, all right. In two cases the
FPIA analysis gave a higher reading than the RIA?

A. Group 4, yes.

Q. All right. Now, my point is this,



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is it valid to draw any conclusion at all with respect to the analysis of post mortem samples in light of the very small number that have been analyzed?

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A. Well, I think I have been sufficiently guarded in my conclusions this morning.

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Q. Well, you have said you were guarded, sir, but you have also said that you would conclude that probably the FPIA is more specific. It's the use of the word "probably" at this point in time that I'm concerned with. In light of the small number of instances where there has been an analysis of post mortem samples, is it fair to draw any conclusion at all at this stage?

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A. I think we have to look at that number and then it's an individual's decision on the way he views the situation. So, I can only give you my decision. Your decision may be different. My view of the material is that there are, out of these 37 patients, there are in fact 12 patients that had results lower by the FPIA than by the RIA. There were only two that had results higher by the FPIA. So, the ratio there is 12 to 2.

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Then if we look at the neonatal study in which five patients had their digoxin, apparent



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digoxin concentrations measured by both technologies, all five were -- well, I'm sorry, I stand correct on that. In two of the five, the results essentially were the same, and in three of the five the results by FPIA were lower than the RIA results and in none of the five was the reverse true.

Q. Well, in the case of post mortem samples, the reverse was true in two cases?

A. In two out of 14 cases.

Q. But my point is, the very fact that you are coming up in such a small number of samples with different conclusions, does that not really leave us in a state that at this point it is just not valid to be drawing any conclusions at all?

A. That's your reading of the data and my reading is a little different.

Q. So, to be clear, on your reading you are prepared to say that it is probable that the FPIA will give - it is more specific and will give a lower reading in cases of patients not on digoxin?

A. With the evidence in front of me, yes.

Q. Notwithstanding the number of cases that we're dealing with?

A. Altogether we have 15 in which



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the FPIA is lower than the RIA and we have two in which the reverse is true.

Q. Well, I put it to you, you will be a lot more comfortable with your conclusion, whatever it is, once hundreds of these have been done?

A. That's correct.

Q. And once hundreds have been done, I put it to you that you would be prepared to change your conclusion if that was warranted?

A. Certainly.

Q. Now, if I could just ask you about the reference in Exhibit 25 on the last page to the HPLC analysis that was done. Perhaps I could show you my copy.

The only question I have with respect to this is that that would appear there was only one lab that reported on that particular type of test?

A. With HPLC?

Q. Yes.

A. Yes, correct.

Q. And in light of the fact that there was only one lab that reported on it, really, again, would it not be fair that it is impossible to draw any conclusions with respect to the accuracy or inaccuracy of that method as used by that lab?



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A. Well, as used by that lab one can certainly draw some conclusions. The results were abysmal by that lab. So, I think on that particular sample, that lab performed poorly.

Q. All right.

A. If I could -- I'm sorry.

Q. I'm sorry, maybe this will be what you're coming to. Before you could take the conclusions beyond that particular lab, you would have to know much more about the technique used and the detector used?

A. Correct. One could draw conclusions only to that lab, the lab that used that technique. I have, as I have expressed already, my own reservations about the use of HPLC for the measurement of digoxin concentrations in a therapeutic drug monitoring scene.

Q. Now, with respect to Substance X and HPLC, we can all agree that Substance X is unknown and that it could be similar to digoxin in structure, and if it is similar to digoxin in structure, would that be the worst case from an analytical point of view in trying to identify it?

A. Yes, the more similar it is the more difficult it will be to separate it chromatographically. Now, as I have explained, one can



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achieve identification notwithstanding this fact
through the use of a mass spectrometer.

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Q All right. There are other
compounds which are similar to digoxin, I understand,
such as, digitoxin and dihydrodigitoxin and dihydro-
digoxin?

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A Yes.

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Q And would you agree with me that
those compounds can be separated from digoxin by HPLC?

A Yes, that's true.

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Q And the fact that HPLC has been
able to separate other similar compounds from digoxin,
would it not suggest that that method is one that may
well separate Substance X from digoxin when it's tried?

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A It suggests that, but it doesn't
prove it, and one has to prove it.

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Q Right. And if my understanding,
which is very limited with respect to HPLC is correct,
it uses a column as a separation device?

A It uses a column and a mobile
phase as a separation device. The mobile phase is
a critical component of any liquid chromatographic
separation.

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Q. But am I correct that there are different types of columns that can be used along with the other phase?

A. There are, yes, there are a large number of columns.

Q. And just the two that I have heard about are the reverse phase column and the absorption phase?

A. Yes.

Q. Is it true that these different types of columns separate compounds in different ways?

A. Separation is achieved, it can be in different ways, it depends on what your mobile phase is. If, for example, you add a iron into the mobile phase, then you will in fact be creating an iron exchange column out of the reverse phase column, so that your technique for separation becomes one of iron exchange chromatography. So there are different ways of causing these separations.

Q. So if you used different columns, you can separate the different compounds in different ways, or the same compound in different ways.

A. You could.

Q. Now, if HPLC has been used to



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separate compounds which are similar to digoxin,
and there are different ways of using HPLC to
separate compounds in different ways: if two
different columns separate a compound does that
not suggest that that particular approach is
likely to be one that provides some greater degree
of accuracy in terms of ensuring that one has
separated the compounds?

A. Yes, I agree with you it
increases the chances that we might be able to
separate or be able to tell whether we have
separated digoxin from substance X. It may not
be able to prove it, though.

Q. Would you agree that it would
be unlikely that substance X and digoxin would
come off the two different columns at the same time?

A. They may.

Q. They may, but how likely do
you think that would be?

A. I think it is probably unlikely.

Q. Now, with respect to Mr.
Cimbura, you sat through his evidence?

A. Some of his evidence.

Q. You were not here for all of it?



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A. No.

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Q. And is it fair to say at

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this point in time, I am asking you if this is

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a fair statement of your position with respect

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to him. Would it be fair to say at this point

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in time that in terms of you giving any opinion

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on his method and the accuracy or inaccuracy of

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it, that in the evidence that he has given so far

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you did not get the data required to allow you to

give such an opinion?

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A. I think that is true in an

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overall sense, some data was given which I could

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comment on.

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Q. I appreciate that you have

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questions about some of the procedures that he

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used based on some of the data that was given.

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Or that you would at least like to know more about

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certain aspects of it. In terms of being able to

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give an opinion on the accuracy or inaccuracy of

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the results of his investigation at this point in

time, is it not fair that you do not have all the

information you would need to have?

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A. No, I think that is in-

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appropriate. In other words, I feel that there are

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aspects that I would be as a scientist critical of at

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this point in time. There are aspects that I wouldn't want to address at this point in time because I don't have the data, as you pointed out.

Q. Well, I assume as long as there is one aspect that you don't have the data with respect to, that in terms of giving an overall opinion you would want that data before you ventured such an opinion.

A. I don't think that is necessary at this point in time.

Q. What is it that you don't think is necessary?

A. To get all the data. I think it is important to get the data to have a critical look at the entire methodology, aspects have been mentioned which I personally am not happy with.

Q. At this point in time when we are dealing at this phase of these hearings with methodology, there is data that you do not have from Mr. Cimbura that you would need in order to give that type of an opinion on his methodology.

A. To evaluate the entire method, yes.

MR. HUNT: Those are all my questions. I have. Thank you, Mr. Commissioner.



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THE COMMISSIONER: Thank you. Mr.

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Rosenberg.

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MR. ROSENBERG: No questions.

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THE COMMISSIONER: Mr. Shinehoft.

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MR. SHINEHOFT: I have no questions,
Mr. Commissioner.

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THE COMMISSIONER: Miss Jackman?

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MS. JACKMAN: I was going to wait
until after Miss Kitely.

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THE COMMISSIONER: You were going
to wait until what?

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MS. JACKMAN: Miss Kitely and I
agreed that she go first.

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THE COMMISSIONER: Oh, I see. All
right, Miss Kitely.

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MS. KITELY: Thank you, Mr. Commissioner.

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THE COMMISSIONER: The only problem is
I might forget you.

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CROSS-EXAMINATION BY MS. KITELY:

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Q. Dr. Soldin, I am assuming
since the slide projector is still here that we
didn't see all the slides yesterday, do you still
have a couple left?

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A. Yes.

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Q. Could you go through them for

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A. Yes.

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THE COMMISSIONER: That is exactly the kind of question I would hope you would have got rid of at the session yesterday. You don't have any idea what is in them, you have no idea whether they will help us or not.

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MS. KITELY: Yes, I do know what is in them, sir, and I think they will be helpful. I thought it easier for Dr. Soldin to give the explanation than me to try to drag it out of him.

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THE COMMISSIONER: You did go through them with him?

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MS. KITELY: I went through it with him at the break.

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THE COMMISSIONER: Yes, all right.

THE WITNESS: I will be very brief. The slides pertain to the appropriate sampling time for digoxin analysis.

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THE COMMISSIONER: I'm sorry, they pertain to the appropriate what?

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THE WITNESS: Sampling time. This slide shows the time that it takes for digoxin to distribute between the tissues and plasma after the administration of an IV dose of



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the drug. As you can see, it takes approximately six hours for equilibration between plasma and tissue, and it is for that reason that sample should not be drawn prior to six hours for the measurement of digoxin. The ideal sampling time in a therapeutic drug monitoring laboratory for really all drugs, there are one or two exceptions, should be, the sample should be drawn just before the next dose of the drug.

Now, if digoxin is administered every twelve hours the sample should be drawn just before the next administration. If digoxin is given orally instead of intravenously, it also takes approximately six hours for that equilibration.

What I wanted to convey with this slide is that when a drug is administered at intervals equal to its half life, it takes approximately five half lives to reach a steady state plateau. What we have here is an increasing curve, that is, the concentration of digoxin is increasing with time as the digoxin administration continues and the important parameters here are that the steady state concentration, that is, where we have a plateau, the steady state concentration for most drugs is directly related to the drug dose.



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So if you double the drug dose, then you tend to double the steady state concentration, and if you halve the drug dose, then you would halve the steady state concentration.

Now, there are exceptions to that rule again. So the optimal sampling time, therefore, should be at steady state. One should wait until the patient is at steady state, which means one should wait five half lives after the commencement of therapy, unless one uses a digitalizing dose or a higher dose to start the therapy, in which case one could start monitoring earlier.

Q. Just as the copies of your slides were made available yesterday, Dr. Soldin, might we have copies of those two slides?

A. Certainly, yes.

Q. Now, Doctor, when Dr. Ellis was on the witness stand he was asked about the multiplier effect and that was as between serum and tissue on the one hand and pre and post mortem on the other hand. Were you present for that evidence?

A. Yes, I was.

Q. And he produced a couple of articles which have been made Exhibits 19 and 20 after



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he got off the witness stand.

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A. Yes.

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Q. And you have seen those
articles?

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A. Yes, I have seen them.

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Q. I indicated to you in the
break that I intended to ask you about those because
Dr. Ellis said you could help us with further informa-
tion about the multiplier effect.

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A. Yes.

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Q. And I gather that you are
not very comfortable with that and that you feel
there is someone who is more able to answer questions.

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A. I think that the best person
to ask about that particular effect, or a very good
person to ask would be Dr. Steve Spielberg from our
division of clinical pharmacology.

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Q. Why do you think he would be
the best person?

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A. Well, he has done a lot of
reading in that area and I have had discussions with
him on it. So I think you will get up to the minute
data from him of his evaluation.

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MS. KITELY: Mr. Commissioner, we
asked last evening whether Dr. Spielberg would



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be called and I don't know that we got a positive reaction, but I will certainly waive any questions of this witness if Dr. Speilberg is coming.

THE COMMISSIONER: I don't want to make too many rash promises because sometimes we put a witness in for one question and he stays a week.

MR. LAMEK: Mr. Commissioner, it is our expectation that Dr. Speilberg will be called as a witness but he's not available at the moment.

MS. KITELY: On that understanding I will leave the topic, sir.

THE COMMISSIONER: It is not exactly a promise in blood.

MS. KITELY: In serum.

THE COMMISSIONER: In serum, good for you.

Q. Well, Mr. Strathy was asking you some questions about the effect of some other drugs such as quinidine. I note included in the documents that were placed on the table this morning was, I guess it is called an abstract from a magazine, is that correct?

A. Correct.



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Q. Now I understand you to be the author of an article about "Interaction of Digoxin with Co-administered Drugs". Is that correct?

A. Yes, I am one of the co-authors.

Q. What we have is an abstract, not the entire article, obviously.

A. Yes.

Q. From what magazine is this abstracted?

A. As it states "Clinical and Investigative Medicine".

Q. Would the article be available?

A. I am sure you could get that - or I could get it for you.

MS. KITLEY: Dealing with the abstract, Mr. Commissioner, I wonder, until we get the actual article, if the abstract itself might be marked as the next exhibit?

THE COMMISSIONER: Exhibit 28.

--- EXHIBIT NO. 28: Abstract from "Clinical and Investigative Medicine".

MS. KITLEY: Q. Now from reading just the abstract I gather that you looked at four drugs specifically and they would appear at the beginning of the article quinidine, verapamil, amiodarone and --



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A. Indomethacin.

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A. Yes.

Q. Namely that quinidine, verapamil and amiodarone have a tendency to show elevation whereas the other drug tends to show a decrease - has that simplified it?

A. No.

Q. Is that an accurate reflection of the conclusions that you drew?

A. No, you have got it wrong. The three drugs have been shown, quinidine, verapamil and amiodarone, have been shown to have a effect on digoxin clearance by the kidney and through that effect they cause or can cause an elevation in the serum or plasma digoxin concentration.

Q. They can cause what?

A. An elevation, an increase.

Q. As much as double, is that what you said earlier?

A. Well, approximately.

Now, the other drug, indomethacin, works differently. Essentially it decreases the



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GFR which is the Glomerular Filtration Rate and as a result of a decreased GFR digoxin is removed also to a lesser extent and therefore this leads again to an increase in digoxin serum concentration.

Q. So they all - the administration of all those four drugs can result in an increase?

A. Yes.

Q. And when Mr. Strathy was asking the questions earlier and you indicated it might be as much as double, were you referring to the study which is the substance of that abstract?

A. The actual values which are given here for indomethacin resulted in an increase from 2.2 to 3.2. Those were the mean increases.

Q. That is right in the middle of the paragraph, is that right?

A. Yes.

Q. Mr. Hunt, who immediately preceded me, asked you about Mr. Cimbura's methodology and I understood you to say that while you do not have a lot of data but have simply general information at this point in time, that there were some aspects that you would not like to comment on now but some that you could?

A. That is correct.



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Q. Mr. Hunt did not ask you what you could comment on so I am now asking you what you feel comfortable to comment on about Mr. Cimbura's methodology?

A. There were several areas. The one area would be, if my understanding is correct, Mr. Cimbura indicated that he did not make a correction for recovery studies which he said that he performed.

THE COMMISSIONER: Did not make a correction for the recovery?

THE WITNESS: For the measured - yes - in other words, the recovery as measured apparently in his studies, I have not seen his data, but he stated that the recovery in his studies was below 100 per cent. I think he mentioned a figure of 85 per cent and again my comment there would be that I think it is appropriate to correct for losses in an analytical procedure.

When we do similar studies on the drugs which we measure if the recovery is, let us say, 50 per cent, then we make such a correction.

It is very important, talking about recoveries, to know whether or not a recovery is consistent from sample to sample. So that one, when one then deals with an unknown sample, one can use



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the correction factor. So if we take let us say, 10 samples of whole blood from different people and if we found that the recovery of digoxin from these samples was 85 per cent in every case then we could correct by 100 over 85 in the unknown samples because we would have some data showing that the recovery of digoxin was consistent from sample to sample.

If we do not have that data then one cannot - one does not know. On the other hand, if the data showed that the recovery varied from sample to sample, then it would be extremely difficult to make a meaningful correction.

Q Are there any other comments you can reasonably make at this point in time about Mr. Cimbura's methodology?

A. Well, two small comments - if I recall he stated that recovery studies of some sort had been carried out on blood and tissues but not on serum. I think that is what he said. I think that in my opinion one should always carry out recovery studies on, let us say, serum, if one is then going to report results on serum so that if we intend to develop a method which can be used for the quantification of digoxin in serum we should have



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assessed its recovery in serum. If we are going to use that method for the measurement of digoxin in whole blood, we should have assessed its recovery in whole blood and if we are going to use it for the measurement of digoxin in heart tissue we should have used it to do recovery studies in heart tissue. As I have indicated, again these are my personal views, I think one should do several studies showing that the recovery does not change from sample to sample.

Getting away from the recovery area, my experience with saline standards, which I think Mr. Cimbura stated that he used, although the point when he switched from serum standards to saline standards is not at all clear to me, from what I heard.

But my impressions of the use of saline standards, again I would think that the standards should be in the same matrix as the samples that have been tested. That is, if we are testing samples in serum then the standards should be in serum and if we are testing samples in whole blood the standards should be in whole blood.

If this does not occur, my experience with the RIA procedure, shall we say, as used at Sick Children's, is that errors may arise as a result



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of using saline standards instead of serum-based
standards in the analytical procedure.

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That is true not only for digoxin but
it is true for many assays so wherever possible we
use standards which are in the same matrix as the
samples being analyzed.

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Q You used the word "matrix" and
for those of us who are novices, that simply means
the substance into which you put the digoxin for
the standard?

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A That is right, yes.

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Q On this very point, have you done
some work at the Hospital?

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A We have developed many drug
assays. If you are talking about with respect to
digoxin, we have done, obviously we have looked at
the factor of using saline standards versus serum-
based standards in many of our drug assays, but we
have also looked at with digoxin in respect to the
RIA assay.

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Q Specifically on the RIA assay
of digoxin, have you analyzed the effect of saline
in the standard?

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A In our assay?

Q Yes.



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A. I would point out that the situation in Mr. Cimbura's lab might be completely different. He may well have evaluated saline standards fully and found that they are the best type of standards to use for his particular assay, I do not know.

Q. Assuming we enquire of him when he is next here whether he did or not, for the moment can you tell us about the conclusions of the testing that you did, comparing the saline matrix for the standard?

A. In our system it caused a skewing, is perhaps the best way to say it, of the standard curve so that it changed essentially the slope of the standard curve. What this would give rise to in our particular system is that we would have reported results which were too high in the low areas of our standard calibration curve and results which were too low in the high areas of our calibration curve.

Q. Can I use some numbers to illustrate that, Dr. Soldin? Am I correct that you were measuring on a calibration of 0 to 5?

A. Yes.

Q. Do I understand that if you measured and got a reading between 0 and 2 that because



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of the saline that the result was falsely elevated
and that it ought to be something like 1.5?

A. It could have been out by as
much as a factor of 1.5, yes, in our system.

Q. I just want to simplify this as
much as possible and use some numbers. Am I accurate
in saying that if you tested and got a result of 2
that because of the saline factor the more accurate
reading ought to be 1.5 - ought to be with some
deviations - but it is lower than 2, that is the
point?

A. Yes.

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Q. And if, on the other hand,
you measured and got a reading of four that, in
fact, it ought to be perhaps 4.5 or 5?

A. That's correct, yes.

Q. Now, is there any written
summary or report about this analysis of this saline
effect that you conducted in the hospital?

A. No, there is no written
summary or report on that.

MS. KITELY: Those are all my questions,
sir.

THE COMMISSIONER: All right.

Ms. Jackman, are you now ready?

CROSS-EXAMINATION BY MS. JACKMAN:

Q. Doctor, I just have a couple
of short questions following up from Ms. Kitley.
She was talking about the testing using saline
standards. If you were using an extraction process
before you tested such as, HPLC and RIA, do you
think that would have any effect on the distortion
that you've talked about?

A. Well, an extraction process
would effect first of all the recovery, and this
is what we are really talking about in Mr.
Cimbura's case. From the evidence it's not clear



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whether Mr. Cimbura uses the extraction process for his saline standards as well as for his patient samples. He may and he may not, I am sure that will come to light later.

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Q. Doctor, have you ever tested tissue samples?

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A. No. Well, as long as you don't call blood a tissue.

9

10

Q. Are you familiar with the literature or the methods of testing tissue samples?

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A. I am not a forensic scientist, I'm a scientist who has had a fair amount of experience in the measurement of drug concentrations in biological fluids, not in tissues.

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Q. Well, Doctor, would you be able to, based on your experience, say what the concerns would be around analyzing tissue samples, what steps you would have to go through in order to make sure you got accurate readings?

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A. Well, I have never analyzed tissue samples. So, I would rather address myself to something that is perhaps close to that but not the same as it, which is, what study should be carried out in developing a method for serum or plasma, which I have had a lot of experience with, and can



1
2 talk about very competently. Now, if you don't
3 want to hear that then I won't go further.

4 MS. CRONK: Well, Mr. Commissioner,
5 I don't like to interrupt my friend's cross-examina-
6 tion, but the witness has already disclaimed any
7 experience in tissue testing, not once but a number
8 of times throughout his evidence and I would have
9 thought that any questions directed to the appropriate-
10 ness of a particular system versus another for tissue
11 testing is something that Dr. Soldin candidly and
12 immediately recognizes as beyond his purview and
experience.

13 MS. JACKMAN: I will leave it, Mr.
14 Commissioner.

15 Q. Just one other question. Have
16 you ever tested whole blood? I should put it this
17 way. Would you have any concerns about testing
whole blood in terms of readings of digoxin?

18 A. In terms of?

19 Q. In terms of getting an
20 accurate reading of what the level of digoxin is.

21 A. Well, I noticed the forensic
22 literature uses whole blood a great deal. I think
23 there are certain problems attached to the measure-
24 ment of digoxin concentrations in whole blood and I
25



1
2 think it would depend on how that sample is
3 treated.

4 Digoxin itself binds to the red
5 cell and the red cell membrane fairly strongly.
6 The extent of its binding, certainly, is different and
7 dependent upon the age of the patient, as
8 opposed to the digoxin binding in serum, which is
9 very weak. So that if one performed an extraction
10 procedure from serum, I think you might, I am not
11 saying you will, but you might get a different
12 recovery for digoxin from serum than the recovery
13 that you would obtain from whole blood, in which
14 digoxin is bound to membrane. The recovery that
15 you get from them all might be dependent on how
16 much digoxin is, in fact, bound to that membrane
17 which varies, as I pointed out, with the age.
18 It might vary with the length of time that you were
19 to use in the actual extraction procedure. Let's
20 say you were using an organic solvent such as
21 dichloro methane. Those are the only comments that
22 I have to make on that.

23 Q. Could I just ask you one
24 further question on that. When you are talking
25 about the differences in using whole blood or
serum, would the results likely be higher if you



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were using whole blood or lower?

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A. I don't want to go any further

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than I have already gone.

5

Q. Okay, those are all the

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questions that I have.

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THE COMMISSIONER: Thank you.

8

Mr. Young?

9

MR. YOUNG: Mr. Commissioner, I

10

indicated earlier that I didn't have any questions,
but there is one matter that has come to light.

11

THE COMMISSIONER: Yes, all right.

12

CROSS-EXAMINATION BY MR. YOUNG:

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Q. Dr. Soldin, in response to

14

one of Miss Kitley's questions, you stated that

15

Mr. Cimbura did not make a correction for the amount
that he recovered. I believe that is referring to

16

the extraction process, is that right?

17

A. That's my understanding. I

18

may be wrong, but that's my understanding.

19

Q. Would it be correct to say,

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Doctor, that without this correction factor or

21

process that any results that were received would be
underscored?

22

A. They would be lower, yes.

23

THE COMMISSIONER: I am sorry?

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THE WITNESS: They would be lower.

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THE COMMISSIONER: Lower.

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MR. YOUNG: That's the only point I
wanted to make, thank you.

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THE COMMISSIONER: Mr. Ortved.

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MR. ORTVED: Thank you, Mr.

7

Commissioner.

8

CROSS-EXAMINATION BY MR. ORTVED:

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Q. Now, Dr. Soldin, as I under-
stand it, you are the last witness in this preliminary
phase concerning digoxin. I would just like to
summarize, if I might, very briefly, for the assistance
of all of us and for the Commissioner, those cautions
which as a biochemist and as an expert you feel have
to be applied in interpreting levels of digoxin.
Firstly, as I understand it, you have to firstly
consider what the sample is, is that correct?

17

A. Right.

18

Q. And you told us, and I don't
intend to repeat this, that you have to bear in
mind, firstly, is the sample one of serum, plasma
or whole blood, right?

21

A. Yes.

22

Q. And bearing in mind which it
is, that may, to some extent, skew the results.

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A. I am not aware of the difference

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between serum and plasma in the measurement of

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digoxin.

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Q. Right, but as between

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serum and plasma on the one hand and whole blood

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on the other, you may get a skewing of the results.

8

A. You may, although I am not

basing that on my personal experience.

9

Q. I understand that. I am

10

putting my questions to you not just on the basis

11

of your experience, but on the basis of your under-

12

standing of the literature, all right?

13

A. All right.

14

Q. Then, secondly, in terms of

15

samples, under that first heading of samples, you

16

have to be careful as to whether it's a sample of

fluid or a sample of tissue, correct?

17

A. Right.

18

Q. Because, as we have heard here,

19

if it is a sample of tissue, digoxin binds differently

20

to different tissues and you can get very high

readings from certain tissues.

21

A. Right.

22

Q. And, in particular, the readings

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for the myocardium may be in children as high as

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340-odd times that in the serum?

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A. The best person to talk about
that is Dr. Speilberg, I think.

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Q. But that's what the literature
says.

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A. Right.

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THE COMMISSIONER: Yes, Ms.
Cronk.

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MS. CRONK: Excuse me, Mr. Ortved.
Again, with hesitancy I interrupt, but I have two
problems with the line of questioning, Mr.
Commissioner.

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The first is, once again, and I did
not rise at my friend's first question but at the
second, it seems to me he is now moving into the area
where he is asking this witness to comment on matters
related to tissue testing and experience on tissue
testing. Again, we have had a disclaimer from Dr.
Soldin.

19

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THE COMMISSIONER: Well, he's not going
that far. All he's saying, it is a question to be
applied whether it is fluid or tissue, which is
the sort of question if he asked me I think I could
answer.

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MS. CRONK: Well, but the second



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2 difficulty or the color to the issue, Mr. Commissioner,
3 and perhaps simply it can be made clear ---

4 THE COMMISSIONER: When it gets into
5 precisely what the difference is, then I will stop
6 him, but right at the moment he is merely saying
7 that you apply some caution if you don't interpret
8 figures for fluid and tissue the same way.

9 MS. CRONK: Well, I think the point,
10 Mr. Commissioner, is that Mr. Ortved introduced this
11 line of questioning by speaking about the interpreta-
12 tion of results and Dr. Soldin has said on any number
13 of occasions that that, again, is not a matter that
14 is within his experience or, indeed, within his
15 responsibility and if he is being asked to comment
16 in that context with that preface, on question of
17 this kind, I have a great difficulty with him being
18 permitted to do so.

19 THE COMMISSIONER: Yes, all right.
20 Well, I won't be taking it that way, though, Mr.
21 Ortved, so you carry on.

22 MR. ORTVED: Thank you, Mr.
23 Commissioner.

24 Q. Then under my second heading
25 I have site of the sample. I take it in your
experience and as a biochemist that is something



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that has to be carefully considered.

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A. It depends what sample you are talking about. If you are talking about autopsy samples, it is important.

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Q. That's right.

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A. If you're talking about samples drawn from an intravenous puncture or from a capillary heel stab or finger prick, I think there is very little difference between the latter three.

10

11

12

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Q. Right. But speaking of autopsy samples for the moment, and autopsy samples in serum obtained on autopsy, the site from which that sample is taken is of importance, correct?

14

15

A. The literature would indicate that, yes.

16

17

18

19

Q. Right. And then, thirdly, as I understand it, and you have talked about this very recently in your evidence, the time after the administration of the dose is of importance?

20

21

A. It's crucial.

22

Q. Right.
And that can vary particularly depending upon whether the dosage is intravenous or oral.

23

24

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A. Oh, I think what I said was it



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2 was independent, essentially, of whether the
3 dosage was IV or orally, that one should wait for
4 the ideal sample, which is the pre-dose sample in
5 both cases.

6 Q. Precisely. But depending
7 upon whether the administration is intravenous or
8 orally, that can have an effect if the sample is
9 taken before equilibration is reached.

10 A. Certainly.

11 Q. Then, fourthly, and this is
12 something that you probably know from the literature
13 as opposed to your own experience, whether the
14 sample is ante mortem or post mortem is of importance.

15 A. Right.

16 Q. And if it is post mortem there
17 may be a factor involved?

18 A. Yes.

19 Q. Fifthly, the age of the
20 subject is of importance.

21 A. In what regard?

22 Q. Well, in the regard that we
23 have heard here from Dr. Seccombe and from yourself
24 that there may be non-dig like substances that may
25 impact on results.

A. Correct.



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Q. Sixthly, something you have spoken about yourself, various drugs may interact and have an effect on a level?

A. Yes.

Q. That is something that has to be looked at and if possible, eliminated?

A. Right.

Q. And then lastly, something we have heard a great deal about here, the actual test itself may be a factor?

A. Yes.

Q. There is a variation between the accuracy of tests.

A. They could be, yes.

MR. ORTVED: Those are my questions.
Thank you.

THE COMMISSIONER: Miss Solomon.

MS. SOLOMON: No questions.

THE COMMISSIONER: Mr. Olah.

CROSS-EXAMINATION BY MR. OLAH:

Q. Just following up on a question, Doctor, that was asked of you. As I understood your evidence the absence of factoring in 85 per cent instead of 100 per cent recovery level means that you are actually getting low levels of readings



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rather than the true higher accurate levels?

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A. That is if one makes an

adjustment for recovery as I state it. The issue

though is one of - there is a further complexity

to this problem. That is does Mr. Cimbura employ

an extraction procedure for standards, that is the

same procedure that he employs ---

Q. I'm sorry, could you repeat

that?

A. Does he employ an extraction

procedure on standards that is the same procedure

that he employs when he does analysis on tissues

or blood. You know, if he does employ an extraction

procedure on standards maybe the extraction is

different.

Q. Are you suggesting that there

should be an extraction procedure applied not only to

the sample but to the standard also?

A. I am suggesting - again I want

to get away from tissues now and talk about serum and

plasma which I have had experience with. If I wasn't

making an extraction procedure for the isolation of

a drug from serum or plasma that ideally my standard

should follow the same route of analysis.

Q. Following that line of logic,



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2 are you suggesting that HPLC should also be done to
3 the standard?

4 A. No question about it. If you
5 are going to standardize your system then the
6 standards must go through the exact procedures that
7 the samples go through and ideally the standards, in
8 my experience, should be in the same matrix as the
9 substance as you are testing it.

10 Q. Now, getting back to that issue
11 that was raised with you by Miss Kitely. I understood
12 your evidence to be that in effect that the higher
13 ranges the use of saline instead of plasma or some
14 fluid in essence understated the results. Do you
15 remember that evidence?

16 A. I said - well, it depends what
17 you call a higher value, values between 3 and 5
18 were falsely, would be falsely lower.

19 Q. Understated?

20 A. Understated.

21 Q. What about if we were dealing
22 with levels substantially higher say in the range of
23 60 or 70 nanograms per millilitre?

24 A. Right.

25 Q. Could you help us in that regard?

A. Well then you would do a dilution



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2 in order to get the sample to read within the zero to
3 5 because that is your calibration curve, if you have
4 a calibration curve that goes from zero to 5, if the
5 sample reads 60 you have to dilute that sample,
6 depending on what dilution you choose your answer
7 then might differ. If you choose a dilution that
8 gives you a result of 3.5 that would - and I am
9 talking about our particular assay system, that
10 should be in other words higher than using the
11 procedure that we use, higher than 3.5. If one got
12 a result between zero and 2 that result would be
falsely higher.

13 Q. What I am trying to determine
14 is this. Is there some sort of a multiplier effect,
15 or some sort of an impact when you are looking at
16 fairly high levels, that is the difference, the
17 use of saline, is that magnified as you get higher,
or is it a constant?

18 A. I can't answer that for
19 Mr. Cimbura's situation and for the experiments
20 which he has done. All I can do is address that
21 question to the studies we have done. What I am
22 trying to indicate to you is that whether the result
23 is falsely high or falsely low depends on where it
24 would fall in our calibration curve. If it fell in
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2 the lower range of our calibration curve, right, it
3 would be falsely high. If it fell in the higher
4 range it would be falsely low, now that is in our
5 particular assay, and the situation may be quite
6 different ---

7 Q. As I understood your evidence
8 the time it takes you to carry out an RIA sampling
9 is somewhere in the range of about two to three
10 hours?

11 A. An RIA, yes.

12 Q. I think you have also indicated
13 that you have had extensive experience with HPLC?

14 A. That's correct.

15 Q. But that was in non-dig situations?

16 A. Yes.

17 Q. Bearing in mind that experience,
18 how long do you feel that an HPLC application with
19 respect to dig would normally take?

20 A. I have never done one so I would
21 have to draw on my experience with other drugs.
22 Assuming that one does an extraction procedure, which
23 we do for many other drugs, followed by evaporation
24 of the organic solvent, followed by chromatographic
25 state, I think that the HPLC procedure certainly
can be accomplished within perhaps an hour for a



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single sample.

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Q. Were you here for the evidence

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of Mr. Cimbura in which he indicated that it normally

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took him somewhere in the range of one and a half

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to two days to carry out this two-step process,

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bearing in mind there was also an extraction procedure

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in there? Is there any explanation - maybe we

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should go back one step, how long would the

10

extraction process - are you familiar with the

11

extraction process he talks about?

12

A. Yes.

13

Q. How long a process is that?

14

A. Well, I am not, I don't know

15

how he applies it. The extraction process is using

16

organic solvents and they tend to be fairly quick,

17

short extraction procedures.

18

Q. He was extracting as I understand

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for metabolites.

20

A. I am sorry?

21

Q. He was extracting metabolites

22

as I understand here?

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A. Yes.

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Q. And also other dig-like

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substances?

A. Well, whatever he is extracting.

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2 But any extraction procedure you know we use one
3 for example when we measure theophylline by HPLC.
4 You take a sample, you add the organic solvent, you
5 vortex it or shake it, that is the equivalent for
6 a certain time period. You centrifuge, you then
7 separate the organic solvent and you then evaporate
8 that. Now for the majority of solvents that whole
9 procedure can be accomplished easily within 30
minutes.

10 Q. 30 minutes?

11 A. For the majority of solvents,
12 not for all.

13 Q. I guess what I am driving at
14 is this. Given the time spans that you have mentioned
15 to us today, do you have any explanation as to why
16 it would take Mr. Cimbura one and a half to two days
to carry out the totality of the procedure?

17 A. No, I have no explanation.

18 Q. Does that strike you as
19 unusual?

20 A. I don't know what he is doing.
21 I would say in my laboratory it would be strange.

22 MR. ORTVED: Thank you. Those are
23 my questions.

24 THE COMMISSIONER: Mr. Shanahan.
25



CROSS-EXAMINATION BY MR. SHANAHAN:

Q. Just very briefly, sir. As I understand it here, if I were to come to you in the hypothetical and tell you that Dr. Cimbura has come up with, or had come up with a very high digoxin reading. Based on the observations that you have made with respect to his methodology here, would I be right in concluding then that even that very high reading, because of two factors that we will go into, that very high reading may even be inaccurate insofar as it is just too low?

A. There are - it may be too low. I think there are certain circumstances which possibly may cause it to be too high but I cannot address those because I don't know enough about Mr. Cimbura's method.

Q. What you do know, if you were for instance to have an average recovery rate of 85 per cent, if you were to correct that, that would be one factor that may make those high readings even higher?

A. Correct.

Q. And second of all here, with respect to the use of the saline standards that you made comment on, that the high readings got off the



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saline standards may in fact also be skewered to
the effect that they were made too low?

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A. Well, depending how he treats
the saline standards, and depending on the recovery
from the saline standards, the results may be too
low or too high, that is why I am edging on that one.
I don't know what he does and I would rather not
address the issue until I do know what he does.

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Q. One final thing then, you can't,
as I understand it, on the calibration you have got,
you cannot get a reading we will say of 60 or 70
nanograms, what you do is you get a reading between
zero and 5 and because of the dilution process you
are able to get a final exact reading, is that right?

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A. Yes.

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Q. You said it was out by a factor
of 1.5 possibly, would that be of a diluted sample?

24

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A. That is on the diluted sample,
it would then be multiplied by whatever the dilution
factor is.

Q. All right, my question then is
as you would multiply to eventually get your reading
we will say of 60 or 70 nanograms are you not then
also multiplying that error factor of 1.5?

A. Well, let's take a hypothetical



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example. If you had a concentration of 2 and had the dilution factor of 20 then that should be 40 nanograms per millilitre.

Q. Yes.

A. If indeed that was falsely high and the results should have been 1.5, then the two results should be in fact 30 nanograms per millilitre instead of the 40 nanograms per millilitre which is the one that you would have found.

Q. So that is an area where it would be falsely high?

A. Yes.

MR. SHANAHAN: Thank you, sir, I have no further questions.

THE COMMISSIONER: Mr. Labow.

CROSS-EXAMINATION BY MR. LABOW:

Q. Dr. Soldin, if I understand your memorandum to Dr. MacLeod, one of the reasons you favoured the FPIA method over the RIA method has to do with the American Association for Clinical Chemistry Study that you included as your last page.

THE COMMISSIONER: What is the last exhibit?

THE WITNESS: Yes, that is one of the items.



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MR. LABOW: Q. If I could just refer to that page for one moment.

THE COMMISSIONER: Which exhibit is this?

MR. LABOW: Exhibit 25.

Q. Now the criticism that I drew from your evidence is that there is a much wider scatter using the RIA method and a greater variability?

A. Between the laboratories, yes.

Q. Between the laboratories?

A. Yes.

Q. Could the fact that nine times as many laboratories reported using the RIA method account for the fact that there was a much greater scatter? In other words, some of those laboratories were not terribly proficient?

A. Yes, it would account for a difference in the minimum and maximum values that the standard deviation would take into account the number of the laboratories and so that would sort itself out so to speak.

Q. But wouldn't the identical mean result indicate that basically these two tests give the same results?

A. In good hands the two tests



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give the same result on that sample.

MR. LABOW: Okay, that's fine,
thank you.

Now, I do have one question for
Commission Counsel. Is Dr. Soldin going to be
returning to give any specific results?

THE COMMISSIONER: He doesn't have
any I don't think.

MR. LABOW: I thought he did have
one.

THE COMMISSIONER: My understanding is
he did not do any of the tests upon the babies with
which we are concerned.



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THE WITNESS: I did none of the tests but I was on call on one of the weekends when two of the children died.

MR. LABOW: And you supervised?

THE WITNESS: And therefore was involved in supervision over that one weekend.

MS. CRONK: That is my understanding, Mr. Commissioner; and we may need to bother Dr. Soldin again, if that is the case.

THE COMMISSIONER: The answer to that is "maybe" then I guess.

MR. LABOW: My only question for the Doctor is, if we have heard further from Mr. Cimbura regarding his data and his methods, and you do return, I presume you would then be in a position to comment on the overall methodology that he used.

THE WITNESS: Yes, if you ask me.

MR. LABOW: Thank you.

THE COMMISSIONER: I was sort of hope that we would get rid of this general discussion on digoxin at some point, but perhaps not.

Mr. Roland?



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MR. ROLAND: I have no questions,
Mr. Commissioner.

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THE COMMISSIONER: And now what do
you say? Can we complete this before we all die of
starvation?

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MS. CRONK: I'm going to be a little
while. I suggest we return and do it after lunch,
Mr. Commissioner.

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THE COMMISSIONER: How long do you
think you will be, about half an hour?

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MS. CRONK: Yes, I would think so.

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THE COMMISSIONER: What do you say
we come back at 2:00 then?

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MS. CRONK: That is perfectly
acceptable, Mr. Commissioner.

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THE COMMISSIONER: Is that satis-
factory to you, Dr. Soldin?

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THE WITNESS: Yes,

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THE COMMISSIONER: All right, we
will come back at 2:00 then - sorry - yes?

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MR. LAMEK: Mr. Commissioner, just
so that I know what I am about for this afternoon,
if we return at 2:00 and we are completed at 2:30
may I suggest that we not embark upon a new witness
on the last hearing day of the week.

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You are quite right, Dr. Soldin is for the time being at least the last of the witnesses on the general area. Dr. Mirkin has to come back. We may hear from Dr. Speilberg; but I propose with the next witness to start getting into numbers of deaths and then immediately thereafter into the medical review of charts and medical evidence of that kind. I would suggest, sir, that it might be more appropriate to start that whole new block of evidence on Tuesday morning, whatever time we end this afternoon.

THE COMMISSIONER: I do not think you will find too much objection from anyone to that proposal. As I do not see the immediate end of this Inquiry, I will not object myself.

Is there anything else that you want to say? Do you want to tell anyone else - or are you distributing a program of the evidence for next week?

MR. LAMEK: No, it is really quite easy, though, Mr. Commissioner. I can announce it now.

I propose on Tuesday morning, in light of what you have just said, to call Dr. Anne Gilmour-Bryson who is a consultant to the



Commission, not a medical doctor, and she will give evidence and introduce some charts based on information supplied by the Hospital as to the number of deaths on the Cardiology Wards and the Cardiology Service in the period in which we are interested and in the two immediately preceding nine month periods and the two immediately subsequent nine months periods.

Then I propose to call Dr. Richard Rowe who is the head of the Cardiology Division of the Hospital for Sick Children and who is among the very first people to review charts in the period and to form an assessment as to the explainability of the deaths.

THE COMMISSIONER: Dr. Soldin, thank you, and you are free now - no, you are not quite free, you are free until 2 o'clock if you want to go off. Come back at 2:00 for a grilling by Miss Cronk.

MR. LAMEK: I will be taking Dr. Rowe through a number of the charts that he reviewed over the course of the late summer, early fall of 1980 and early 1981, and the subsequent chart reviews that he did, and I have every expectation that I will be at least three hearing days with



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Dr. Rowe in chief.

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THE COMMISSIONER: Yes, all right.

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That will certainly occupy us next week and

5

probably the week following.

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MR. LAMEK: It certainly will, sir,

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but we will be starting on evidence now going to

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particular deaths that are at issue.

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THE COMMISSIONER: All right.

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Whatever happened to the expurgated Atlanta Report?

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MR. LAMEK: It has been discretely

distributed to counsel, sir.

12

THE COMMISSIONER: All right,

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thank you.

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Yes, Miss Kitely?

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MS. KITELY: Mr. Commissioner, in

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light of the evidence of the consultants concerning

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these deaths in the five periods outlined, I'm

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assuming that there is some material that is

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available from which she is going to give evidence.

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Might we have it this week, as opposed to when she
gets in the witness stand? I think it is something

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that we are all very interested in.

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MR. LAMEK: Mr. Chairman, if what

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Miss Kitely is suggesting is that she gets copies

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of the charts before the end of the week, I do not

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have any difficulty with that. On the other hand,
she is not going to be able to do very much to
verify the accuracy of the charts because that is
a whole mass of documentation that has been
inspected by Dr. Bryson at the Hospital. But for
every use the charts may be, there is no reason
why this should not be made available, tomorrow, I
think.

MS. KITELY: Thank you.

THE COMMISSIONER: Anything else?

All right, then, until 2 o'clock.

---Luncheon recess.



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---Upon resuming.

THE COMMISSIONER: Yes, Ms. Cronk?

MS. CRONK: Thank you, Mr. Commissioner.

REDIRECT EXAMINATION BY MS. CRONK:

Q. Dr. Soldin, we are nearing the end. I promise I won't keep you much longer.

You will recall that this morning during cross-examination I believe it was Mr. Strathy's cross-examination, you indicated, according to my notes, that it was only in recent years that the FPIA technique had become available for drug concentration assays. Do I have that correctly?

A. That's to the best of my knowledge, yes.

Q. All right. Can you help me, Dr. Soldin, because I wasn't clear in that exchange, to the best of your knowledge, when did the FPIA technique first become available for digoxin assays?

A. I don't know that I can answer that question properly. I think probably around two years ago.

Q. All right.

A. But one year ago we evaluated



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it.

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Q. At your own hospital a year

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ago?

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A. Sick Children's, right.

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Q. Well, perhaps I could put the

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question this way. During the period July, 1980

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to March of 1981, to the best of your knowledge,

9

was the FPIA technique then commercially available

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on the market?

A. No, it wasn't available.

11

Q. It was not, thank you.

12

Dealing still with the FPIA Method

13

in light of the cross-examination this morning,

14

Dr. Soldin, can you tell me this, if you are able:

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in your opinion, had the FPIA technique, as you now

16

know it, been available during the period July,

17

1980 to March of 1981 and had been used instead of

18

the RIA procedure to conduct digoxin assays on the

19

children with which this inquiry is concerned,

20

would you expect, or would you have expected any

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material differences in your readings that might

22

have resulted?

A. You are talking about the

23

samples that were analyzed by the Hospital for

24

Sick Children, I take it?

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Q. Yes, I am.

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A. I would anticipate that the results would be fairly similar.

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Q. Thank you. And you were questioned this morning as well by Mr. Strathy, I believe, concerning the HPLC method and, specifically, he drew your attention to Exhibit 25 which, as you will recall, is a copy of your memorandum to Dr. MacLeod and the last page of that exhibit. It might help you to have it before you.

11

A. All right.

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Q. I am referring, Mr. Commissioner, to the last page of that exhibit.

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As I understood your evidence, both in respect of questions put by Mr. Strathy and earlier, Dr. Soldin, the laboratories indicated on that chart, if I could call it that, are a reflection of those clinical laboratories which are members of the association that produced those recorded data. Is that correct?

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A. That have enrolled in this program. They would all have enrolled in the Therapeutic Drug Monitoring Program of this association.

23

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Q. All right.



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2 But I had understood, and perhaps
3 I have this wrongly, I had understood your evidence
4 to be that you could not help Mr. Strathy as to how
5 many, if any, forensic laboratories that might or
6 might not be members enrolled in that program, is
7 that correct?

8 A. I cannot help him without
9 asking the people in Washington that question.

10 Q. All right. Do you know here
11 today whether or not any forensic laboratories are
12 in fact members, quite apart from how many?

13 A. I don't. But I would doubt
14 that many are, if any.

15 Q. Do I take it that you have
16 doubts in that regard because this is a membership
17 program set up with a therapeutic drug monitoring
18 purpose in mind?

19 A. Correct.

20 Q. All right. We should not,
21 then, would I be correct in suggesting, Dr.
22 Soldin, take the numbers disclosed on that chart
23 as being indicative of the number of forensic
24 laboratories that may or may not be using the
25 RIA method or the HPLC method or any of the other
techniques outlined on that chart for the purposes



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of digoxin assays?

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A. Right.

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Q. The numbers for forensic

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laboratories may be quite different?

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A. Yes.

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Q. Thank you. You also indicated,

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as I understood it earlier in your evidence, Dr.

9

Soldin, that it would be unusual to couple HPLC

10

with the RIA technique for detection, did I note

11

that correctly?

12

A. It's not commonly employed as

a detector for HPLC, yes.

13

Q. And did I also note correctly

14

that you indicated to Mr. Strathy that that combina-

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tion, if linked together, was a very sensitive

16

process?

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A. If linked together it would

18

provide sensitivity perhaps comparable to the RIA

19

procedure, perhaps a little less, because you get

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dilution of the sample as it progresses through

the column. So, RIA is a sensitive procedure.

21

Q. I am sorry, perhaps I put

22

the question badly. My question to you was, I had

23

understood you to say earlier this morning that if

24

one were to use RIA as a detection method in association

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with HPLC, I had understood you to say that that combination would be a very sensitive procedure or process.

A. Right, it would be, yes.

Q. Can you help us today, or do you have any knowledge, Dr. Soldin, as to the number of forensic laboratories in North America that are, in fact, using that combination for digoxin assays, or do you know?

A. I have no idea.

Q. Thank you. And dealing with the technique that's been described as HPLC MS, mass spectrometry.

A. Yes.

Q. I believe you told Mr. Strathy, if I have it correctly, that you hoped to obtain -- by you, the hospital hoped to obtain funding to permit that method to be tested for digoxin assays in the future, is that correct?

A. That's correct.

Q. Dr. Ellis told us yesterday in evidence, Dr. Soldin, while I believe you were in the courtroom, that to his knowledge I believe he didn't think there was anybody in Canada who had experience in using the MS system for the



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purposes of digoxin assays. Does that accord with
your knowledge of the circumstances?

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A. Dr. Kuksisx at the Best

Institute has certainly had experience with MS with
some of the digoxin compounds. Now, whether it is in
fact digitoxin or other metabolites, I cannot tell
you. It may well not be digoxin. He's had
experience with a number of very similar compounds.

Q. All right. And is his
experience with HPLC and MS as a combination technique?

A. Well, it wasn't three weeks ago.

Q. All right. Well, one can only
be so definite, I suppose, sitting here today, Dr.
Soldin.

A. Yes.

Q. Can you help me with this.

During the period July, 1980 to March of 1981
and for the balance of 1981, to your knowledge, was
there any laboratory of which you were aware that
was using HPLC in combination with the MS
methodology for the purposes of doing digoxin
assays?

A. No, there wasn't.

Q. All right. To your knowledge,
was the HPLC MS technique, in terms of its hardware



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and its design available commercially on the market for digoxin assays during that period of time?

A. Yes, it was.

Q. Can you help me as to when it became available for that purpose?

A. I would refer you to the system that is at the Best Institute is a Hewlitt Packard model, and HPLC/MS system and maybe if you phoned the Hewlitt Packard people they could tell you when that procedure was first introduced.

Now, I personally went and visited their plant in California around '79. It was certainly there in '79. It might have been there a few years earlier. It was newish in '79.

Q. And again -- I'm sorry, sir, have you finished?

A. The best thing is to ask them for the exact date.

Q. Well, perhaps we will do that in the future, but for present purposes so that I am clear as to your knowledge of the circumstances, I am talking now about the HPLC and MS combination for digoxin assays and your understanding that that was available commercially on the market in 1979.



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A. That's my understanding, yes.

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Q. All right.

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A. And possibly earlier.

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Q. And possibly earlier.

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A. Yes.

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Q. But at that time, to your

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knowledge, there were no laboratories which you can identify for us that had acquired it and were using it for digoxin assay purposes?

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A. Right.

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Q. Thank you. You were questioned

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as well this morning, Dr. Soldin, again, by Mr.

13

Strathy concerning the ability of the HPLC method to extract what's been called substance X and, if I

14

understood the exchange correctly, it was suggested

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to you that it had not been possible to date to say

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with certainty that substance X was separated

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following an HPLC, the use of the HPLC methodology.

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Did I have that correctly?

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A. I think that's correct.

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I have just one rider on that and that is, I'm not sure what Dr. Gault is up to in Newfoundland.

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So, he may well have done some work in this area.

22

Q. Well, bearing that in mind,

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would it be a fairer suggestion by me, Dr. Soldin,

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- 1
- 2 to suggest to you that given the state of the art
- 3 as it currently exists and the state of the research
- 4 as has been described in these hearings, it cannot
- 5 with certainty be said today that the HPLC method
- 6 does not in fact separate substance X.
- 7 A. That's right.
- 8 Q. It may separate it?
- 9 A. It may.
- 10 Q. Then again it may not?
- 11 A. Correct.
- 12 Q. And would I be correct as
- 13 well or fair in suggesting that on the state of the
- 14 research as it has been described to us, that in
- 15 any given sampling group that is run through an
- 16 HPLC methodology for the purposes of a digoxin
- 17 assay, substance X may or may not be present?
- 18 A. Right.
- 19 Q. In fact, there would be some
- 20 sample groups borne out by your own experience at
- 21 the hospital that would suggest that substance X
- 22 was not there.
- 23 A. Right.
- 24 Q. Dealing again with the
- 25 questions that were put to you by various counsel
- concerning the, if I can express it this way, the



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2 utility of one digoxin assay methodology as compared
3 with another, would you agree with me, Dr. Soldin,
4 that any scientist, if required to recreate or
5 implement from scratch a methodology for the
6 purposes of conducting digoxin assays, would bring
7 to bear on that problem in settling upon his
8 methodology his experience with other assays?

8 A. Right.

9 Q. Right. Would you also agree
10 with me that if the scientist that I am proposing
11 was creating from scratch such a system and he had
12 20 or 30 years or 10 years or 15 years experience
13 in using particular kinds of assays for the purposes
14 of recording or determining drug concentration levels,
15 he would bring that practical experience to bear on
16 the decision making process as well?

16 A. He would be tempted to do that,
17 yes.

18 Q. Well, would a prudent scientist
19 not rely on the practical experience that he had accumu-
20 lated over the years in making that decision?

21 A. Yes, he would. That would be
22 part of his evaluation. He would have to consider
23 whether or not there were newer or better methods
24 available and then make a value judgment on which
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which to go.

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Q. Yes. And exactly on that

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point, you would agree with me, I take it, that

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there is an element of professional judgment that

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enters into the exercise?

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A. There certainly is, yes.

8

Q. And would you agree with me

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as well that the scientist creating or implementing

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from scratch, if I can use that colloquialism,

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a digoxin assay methodology would also, if prudent,

12

bear in mind the purpose to which the test results

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were likely to be put?

A. Yes.

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Q. So that if a clinical bio-

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chemist or clinical pharmacologist were asked or

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required to implement such a system for digoxin

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assays in your hospital, for example, if prudent

18

he would bear in mind the therapeutic drug monitoring

19

purpose that was associated with creating that

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assay?

A. Yes.

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Q. And similarly, a forensic

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scientist, if required to create and implement such

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a methodology, would bear in mind that in certain

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circumstances there was a likelihood that test

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results might bear the scrutiny of a court of law?

A. Correct.

Q. In questioning this morning from Ms. Kitley, Dr. Soldin, you showed to her a slide indicating, as I had understood it, the optimum sampling time for taking a sample of digoxin. Do you recall showing that slide?

A. Right.

Q. And explaining what it meant?

A. Yes.

Q. And as I understood your evidence, if I made a note of it correctly, you indicated that the best time for many drugs to take a sample for assay purposes was just before the next dose was administered, is that correct?

A. That's correct, yes.

Q. Right. And we know from your evidence that digoxin at the Hospital for Sick Children is administered every twelve hours.

A. Mostly. I believe that to be true.

Q. Well, perhaps I phrased it badly. As a matter of routine it is anticipated that digoxin was administered to those patients



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prescribed digoxin once every twelve hours.

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A. Yes, and a study is currently in progress to evaluate whether or not we should be changing that to every 24 hours.

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Q. All right. Well, the difficulty that I am having, Dr. Soldin, for the purposes of clarification is this: we know from the contents of the Residents' Handbook that we had examined previously, that at Page 365 of the handbook it is indicated that the optimum, perhaps the word optimum isn't used, but the time for the sampling of digoxin is indicated to be between six and eight hours after administration, is that correct?

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A. Yes.



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Q. Is it then to be taken by us that the optimum time for sampling, for taking a sample for digoxin assay is anywhere after six hours up to and inclusive of the eleventh hour prior to the administration of the next dose?

A. No. My opinion is that the optimal time is just before the next dose. The six-hour post dose sample is adequate, but it is not optimal.

Q. So the six-hour time frame I take it then, in your judgment would be the first onset of the steady state?

A. Right.

Q. The earliest time which a sample might safely be taken, is that correct?

A. Yes.

Q. Am I correct then that at any time after six hours up to and inclusive of the very minute before the next dose is administered would be an acceptable time frame within which to take a sample for digoxin assay, in your judgment?

A. In order to interpret the result clinically and make certain judgments on that measurement, yes.

Q. Do I correctly take it from that



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then that the steady state which is introduced at the earliest of the sixth hour after administration of the dose, continues on the same plane for the next six hours until the next dose is administered?

A. You have used I think the wrong term. It is not the steady state, it is an equilibrium that is achieved after the six hours. The steady state concentration was on the other slide and that takes five half lives to achieve for a drug that is given at intervals equal to its half life, approximately five half lives.

Q. Perhaps I have confused the two concepts. My point is this, is there any danger after the sixth hour, after the administration of the dose of digoxin, if one were to take a sample at the tenth hour, or the eleventh hour, is there any danger of further peaking in concentration of the drug, or would a sample taken at any time within that range be acceptable for your purposes on a digoxin assay?

A. In the routine management of patients that are receiving digoxin orally, a six-hour post dose sample would be adequate, but not optimal. It is possible that if a patient, as in one of our cases several weeks ago, they had swallowed a large number



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of somebody else's tablets.

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Q. Yes.

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A. That the concentration may continue to rise for quite some time and indeed it did in that patient. But that is an abnormal situation and not one that is usually present.

Q. Are you saying then, Doctor, that in certain abnormal or isolated situations the drug may continue to peak after six hours?

A. The concentration in this particular patient remained elevated for a long time. Now, I can't tell you because I don't have the graph in front of me when it actually peaked. This was a patient that had taken oral digoxin tablets and a large number of them.

Q. Then returning to your earlier view as I have understood you to express it, and correct me if I am wrong. I understood you to say that in your judgment the optimum time for the taking of the sample for digoxin assay is the hour before the next dose is administered?

A. In a routine therapeutic drug monitoring setting, yes, not in a toxicology setting.

Q. So that is something we should bear in mind in reviewing the contents of the Handbook?



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A. Yes.

Q. You will recall as well, Dr. Soldin, that in your discussions this morning you offered your opinion, as requested, with respect to a number of the procedures followed, adopted by Mr. Cimbura in conducting digoxin assays. You spoke about his extraction process and the standards that you understood he had used.

Dr. Ellis told us in his evidence that in his laboratory in running RIA digoxin assays that he did not use an extraction process on the sample once he received it. Is that the practice as well in your laboratory?

A. We use a protein precipitation step not an extraction process, right.

Q. Let's take that step by step. You told me previously that with respect to the FPIA technique that there was a protein precipitator, or a separation process that was part of the methodology that worked on the FPIA system?

A. Right.

Q. Let's talk about first the RIA assays that you have run in your laboratory. In respect of those have you adopted or made use of an extraction process?



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A. No.

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A. No.

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Q. In respect of the FPIA digoxin assays that you have run, and apart from the protein precipitator component of the process that you previously described, do you make use or have you adopted an extraction process?

Q. Dr. Ellis also told us in his testimony Dr. Soldin, that if he were required or provided an opportunity to modify the Hospital's RIA methodology for the purposes of conducting post mortem digoxin assays, that one of the things that might be included as a modification was an extraction process.

Do you agree, based on your experience with both methodologies, that if one were to adopt either for the purposes of post mortem testing, that you would look to the inclusion of the extraction process as a desirable component?

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A. It may be a desirable component.

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Q. That is something you would want to look at and make a determination on?

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A. Right.

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Q. And do you agree with me, and again I may be expressing this poorly or inadequately



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and if so I would like you to tell me. My understanding of the process, of the extraction process that is utilized by Mr. Cimbura was for the purposes of separating out digoxin metabolites. Does that accord with your understanding of the process he described?

A. Well, he might have used that extraction to separate or to attempt to separate any compounds that would interfere with the digoxin reacting with the antibody. In other words ---

Q. Yes.

A. -- and need not necessarily be digoxin metabolites.

Q. To put it another way if the purpose of using the extraction process is to achieve in the end result a purer sample upon which the assay might be run, would you agree with me that if one were satisfied as to the particular extraction process at hand that would be a desirable end, that is something you would like to achieve before in fact running an assay?

A. In a forensic setting.

Q. I am not asking you to comment on a setting with which you have no experience. In your own setting if you were - the proposition I put



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A. I would evaluate that.

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A. It may be desirable, yes.

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to you was that if you were to moderate or modify either methodology currently in use in the Hospital, be it the RIA methodology or the FPIA methodology, for the purposes of running post mortem digoxin assays, in your judgment would it be a desirable end to introduce an extraction process?

Q. I am asking you in general terms now, the purpose of the extraction process is to achieve in the end result a purer sample upon which the assay might be run. Would you agree with me that in conceptual terms that is a highly desirable end?

Q. It is not necessarily something that one would seek to achieve from the outset?

A. It depends on what the method of measurement is going to be subsequently, it may not be necessary, it may be and it may not be.



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Q. Dr. Soldin, dealing again with the process that we have heard Mr. Cimbura used for his testing, and I would like to be clear on this and in light of some of the answers you gave this morning. As I understand it, in conducting the RIA digoxin assay test that you have conducted or supervised in your laboratory, you have not had occasion to make use of the Beckman antibody, is that correct?

A. I have personally not, but one of the post-doctoral fellows working with me, have.

Q. I'm sorry, I perhaps put the question in a confusing way. You told me previously in your evidence that a post-doctorate candidate working under your supervision had used the Beckman antibody with the system that you understood Mr. Cimbura to have been using, his methodology?

A. Right.

Q. I am talking now about your own, the RIA methodology that was used and is used in your laboratory. Am I correct that you have not had occasion, nor have those whom you supervised, to use Beckman antibody as part of your RIA process,



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is that correct?

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A. I have had occasion, but

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I haven't done it.

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Q. Again, it has not been done?

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A. No.

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Q. Neither by yourself nor by

anyone under your supervision.

8

A. Right.

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Q. Similarly, as I understand it,

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you have not used the Beckman standards in your RIA

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process nor has anyone under your supervision.

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A. In our RIA process, correct.

13

Q. And, of course, neither would

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be used by you or those under your supervision in

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the FPIA methodology because the standards and

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the antibodies that are used on that system are

provided by others?

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A. Right.

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Q. In questions put to you this

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morning, Dr. Soldin, again, with respect to the

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RIA methodology used by Mr. Cimbura as opposed to

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the one in use at the Hospital for Sick Children,

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questions were put to you as to whether or not you

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could afford any explanation as to the time frame,

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the length of time that Mr. Cimbura indicated it took

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for him to conduct a test using the methodology that he had formulated.

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Comparing the RIA Methodology that has been described here as in use at the hospital with what you understood to be the case from Mr. Cimbura's evidence, the methodology he used, would you agree with me that the length of time that it takes to run an RIA assay would be increased first if an extraction process was used?

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A. Yes.

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Q. And would you agree with me that it would be increased in length of time, secondly, if the gamma counter that you are using to calculate the amount of bound digoxin as opposed to the amount of unbound digoxin was not capable of doing readings on more than one sample at one time?

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A. Yes.

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Q. Would you agree with me that the length of time would be increased again if it was considered desirable or proper technique, to leave the gamma counter with the samples sitting over-night to arrive at a calculation the next day that would necessarily increase the length of time?

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A. Yes, that would increase the



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length of time, and it may or may not improve the results.

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Q. It would increase the length of time if that step were undertaken.

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A. Yes.

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Q. In addition, would it be a fair suggestion to you that if a tissue sample were received, and I recognize and I am very sensitive to your lack of experience with tissue testing, but if a tissue sample were received for the purposes of the digoxin assay, would you agree with me that there might be special procedures which would have to be undertaken in respect of the tissue sample before the assay could be run that might again increase the length of time that it would take to run the assay in its entirety?

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A. Yes.

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Q. And mention was also made this morning, Dr. Soldin, of testing on whole blood. I believe this was a question put to you by Ms. Jackman and, again, I wanted to be clear about that.

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Would you agree with me, taking into account your previous evidence, that digoxin assays are not run on whole blood samples at the



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2 Hospital, certainly not in your laboratory and
3 not in Dr. Ellis' laboratory. Bearing that in mind,
4 would you agree with me once again that if in a
5 forensic setting it was considered desirable
6 or necessary that digoxin assays be run on whole
7 blood samples, that there may be procedures that
8 apply in respect of -- I am sorry, I expressed that
badly.

9 Is it, in your view, possible that
10 in a forensic setting it could be considered
11 desirable or necessary for digoxin assays to be run
12 on whole blood, or can you offer us an opinion in
13 that regard?

14 A. It is feasible that may be
15 an important analysis on whole blood in a forensic
setting.

16 Q. I believe you indicated in
17 response to questions earlier this morning that you
18 had personally noted in the forensic literature that
19 they mainly referred to digoxin assays on whole
20 blood.

21 A. Correct.

22 Q. Finally, Dr. Soldin, you
23 will recall that in questions put to you by my
24 friend, Mr. Ortved, this morning it was suggested
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to you that there were a number of factors that one should take into account in running digoxin assays, and of those mentioned were the time of the last dose; the site from which the particular samples had been taken; the method of administration of the dose; the age of the patient; whether the sample was ante mortem or post mortem. Do you recall those factors being put to you this morning?

A. Yes.



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Q. Would you agree with me, Dr. Soldin, that for the purposes of running the digoxin assay itself, for the purposes of utilizing the methodology to arrive at a recording which as a scientist you felt was acceptable in terms of accuracy on the methodology itself, that those factors are irrelevant?

A. I beg your pardon?

Q. All right.

THE COMMISSIONER: Yes, Mr. Strathy?

MR. STRATHY: Mr. Commissioner, I know that we are not bound by the rules of evidence here, but it seems to me that perhaps there ought to be some distinction between the nature of the questions put by Commission Counsel and the nature of the questions put in cross-examination by other counsel.

THE COMMISSIONER: Yes. There may be something to what you say, but when we get around to re-examination, the temptation to lead is almost overwhelming.

MS. CRONK: And for some of us it appears it is overwhelming, Mr. Commissioner.

If I can help my friend, perhaps I will re-phrase it in a less leading fashion.

MR. STRATHY: I think sometimes for



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the witness himself it may be better to hear it in
the witness' own words. I appreciate what Miss Cronk
is trying to do in terms of saving time.

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THE COMMISSIONER: Yes. Just, have
you any comments upon - can we put it this way -
forget everything you have heard today, can you just
tell us if you have any comment upon Mr. Ortved's
list. He had only seven. I put down eight, but
I sub-divided one of his. Eight matters that would
require caution in the testing.

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THE WITNESS: Right. No comment.

MS. CRONK: Q. Without offending
either you, sir, in terms of the proper manner in
which to put the question or my friend Mr. Strathy
or others, can I ask you this, Dr. Soldin? In your
professional judgment is the time at which the last
dose of the drug is administered relevant to the
conducting of a digoxin assay as opposed to the
interpretation of the results of the recording and,
if so, how?

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A. Are you asking me if the time
at which the drug is administered - relative to the
sampling time, that is certainly important.

Q. All right. And similarly with
respect to - is knowing the site from which the



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sample has been taken relevant to you in conducting
the digoxin assay?

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A. In a routine monitoring lab?

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Q. Yes.

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A. Whether the sample is from a
heel prick or a finger stab or a vena puncture, it
doesn't make any difference.

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THE COMMISSIONER: The only point
surely in all of this is that you are saying that it
doesn't affect his ability to do the test, but the
results will be somewhat different. Isn't that the
point?

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MS. CRONK: That is certainly the
point, Mr. Commissioner.

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THE COMMISSIONER: If it is of any
help to you, it is a point that I have already
mastered.

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MS. CRONK: That's the best possible
answer to the question that I could have received,
Mr. Commissioner.

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THE WITNESS: Well now, I don't
agree with the answer.

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MS. CRONK: Apparently we have some
disagreement.

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THE COMMISSIONER: That's why I



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wanted your comments, all right.

THE WITNESS: There is no evidence that I'm aware of whether one gets the sample from a finger prick, a finger stab or a vena puncture the digoxin measurement will be different.

MS. CRONK: Q. Are we clear on at least this, Dr. Soldin, that you are not involved in the interpretation of the results that you achieve on your digoxin assays?

A. To some extent I'm involved because when results are over a certain level I have to notify the right people and my group have to notify the right people. I don't go to the bedside and look at the patient and decide whether or not the patient is toxic. That is done by the clinical pharmacologists.

Q. That's right.

A. And the clinicians looking after the patient. But it is my responsibility to be sure that a message gets to these clinicians quickly.

Q. And can we go this far together, Dr. Soldin, that there are a number of factors which are highly relevant to the cardiologist in interpreting the results of a digoxin assay?

A. Highly relevant, yes.



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Q. That are not relevant to you
in conducting the test.

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THE COMMISSIONER: I'm sorry?

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THE WITNESS: Well, it depends which
factors you are talking about. If the sample for
example, is drawn at an inappropriate time then it's
relevant to me and the test should not be performed.
I am wasting the Province's funding by performing a
test when the result cannot be interpreted.

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MS. CRONK: I think, Dr. Soldin,
and with the Commissioner's concurrence, I will leave
the point there. Thank you.

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THE COMMISSIONER: Yes.

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MS. CRONK: No further questions.

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THE COMMISSIONER: Thank you.
If you are wise, you will make a hasty retreat
before somebody else gets at you, Dr. Soldin. Thank
you very much.

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THE WITNESS: Thank you.

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---Witness withdraws.

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THE COMMISSIONER: Have you anything
further, Mr. Lamek?

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MR. LAMEK: I thought you were
inviting me to cross-examine Dr. Soldin.

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THE COMMISSIONER: No, no I am not.



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MR. LAMEK: Nothing further today
then, Mr. Commissioner.

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THE COMMISSIONER: All right. Well
then, until Tuesday at 10 o'clock.

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MS. CRONK: Thank you, sir.

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MS. KITELY: Mr. Commissioner,
before we rise. At the risk of asking too much of
Commission Counsel, I know that we are going to hear
from the cardiologist next.

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THE COMMISSIONER: No, I think we
are hearing from the mortician.

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MS. KITELY: Yes, and then the
cardiologist. But I rise to ask if Mr. Lamek has
any long term plans he can let us in on. My concern
is that if the nurses, for example, are going to
follow the doctors, then we would like to know that
in terms of timing. If he has other witnesses that
he's going to stick in before he gets to another
client, I want to know that. I know that I can't
pin him down to the date and the time, but a general
frame of reference would be helpful.

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THE COMMISSIONER: Well, he gave a
sort of a program at the beginning, the agenda.

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MR. LAMEK: Yes, I thought I had
tried to do that, but let me reply. I do not

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2 anticipate, I do not expect to call any nurse as a
3 witness for at least four or five weeks. I propose
4 to lead all of the medical evidence on the charts
5 and perhaps the evidence of clinical pharmacologists
6 and of course the evidence as to the particular
7 digoxin measurements, the evidence of clinical
8 pharmacologists as to the significance of those
9 measurements in those cases and those children and
10 then of course we have to call the authors of the
Atlanta Report.

11 Miss Kitley may be assured that her
12 clients are well away from the witness box at this
13 point, many weeks I'm afraid. All that has to be
14 done before I even think of calling a nurse as a
15 witness, Mr. Commissioner.

16 MS. KITLEY: Thank you, sir.

17 THE COMMISSIONER: Yes, all right.
18 I suppose we could mention that we are giving some
19 thought to moving also but I think that will not be
20 until - obviously we will not be able to keep these
21 premises past Labour Day and we now seem to have
22 permission for the large court room at 180 Dundas
23 Street. It is the Ontario Municipal Board place
24 at 180 Dundas and we may be going there some time
25 in August. So, that is an advance warning.



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If you some day come here and find
nothing is going on, it doesn't mean that the
Inquiry is completed.

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MR. LAMEK: Mr. Commissioner, a
rider that if you find nothing is going on and no
one is here.

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---Whereupon the hearing adjourned at 2:35 p.m. until
Tuesday, July 12th, 1983 at 10:00 a.m.

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